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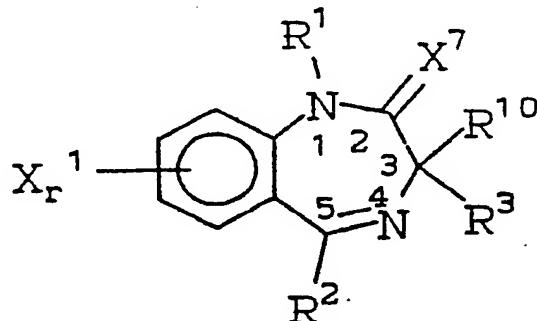
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54 Benzodiazepine analogs for treating panic syndrome and for directly inducing analgesia.

57 Benzodiazepine analogs of the formula:



are disclosed which are antagonists of gastrin and cholecystokinin (CCK) and have properties useful for treating panic syndrome and for directly inducing analgesia.

EP 0 434 364 A2

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BENZODIAZEPINE ANALOGS FOR TREATING PANIC SYNDROME AND FOR DIRECTLY INDUCING ANALGESIA

CROSS-REFERENCE

Starting materials for the compounds of Formula I are prepared and described in U.S. Patent 4,820,834 and B. Evans et al., *J. Med. Chem.* 31, 2235-2246 (1988).

5

BACKGROUND OF THE INVENTION

Cholecystokinins (CCK) and gastrin are structurally-related neuropeptides which exist in gastrointestinal tissue and in the central nervous system (see, V. Mutt, *Gastrointestinal Hormones*, G. B. J. Glass, Ed., Raven Press, N.Y., p. 169 and G. Nisson, *ibid*, p. 127).

10

Cholecystokinins include CCK-33, a neuropeptide of thirty-three amino acids in its originally isolated form (see, Mutt and Jorpes, *Biochem. J.* 125, 678 (1971)), its carboxyterminal octapeptide, CCK-8 (a naturally-occurring neuropeptide, also, and the minimum fully active sequence), and 39- and 12-amino acid forms, while gastrin occurs in 34-, 17- and 14-amino acid forms, with the minimum active sequence being the C-terminal tetrapeptide, Trp-Met-Asp-Phe-NH₂, which is the common structural element shared by both CCK and gastrin.

15

CCK's are believed to be physiological satiety hormones, thereby possibly playing an important role in appetite regulation (G. P. Smith, *Eating and Its Disorders*, A. J. Stunkard and E. Stellar, Eds, Raven Press, New York, 1984, p. 67), as well as also stimulating colonic motility, gall bladder contraction, pancreatic enzyme secretion, and inhibiting gastric emptying. They reportedly co-exist with dopamine in certain mid-brain neurons and thus may also play a role in the functioning of dopaminergic systems in the brain, in addition to serving as neurotransmitters in their own right (see : A. J. Prange et al., "Peptides in the Central Nervous System", *Ann. Repts. Med. Chem.* 17, 31, 33 [1982] and references cited therein ; J. A. Williams, *Biomed. Res.* 3 107 [1982]; and J. E. Morley, *Life Sci.* 30, 479, [1982]).

20

The primary role of gastrin, on the other hand, appears to be stimulation of the secretion of water and electrolytes from the stomach, and, as such, it is involved in control of gastric acid and pepsin secretion. Other physiological effects of gastrin then include increased mucosal blood flow and increased antral motility, with rat studies having shown that gastrin has a positive trophic effect on the gastric mucosa, as evidenced by increased DNA, RNA and protein synthesis.

25

Antagonists to CCK and to gastrin have been useful for preventing and treating CCK-related and/or gastrin-related disorders of the gastrointestinal (GI) and central nervous (CNS) systems of animals, especially of humans. Just as there is some overlap in the biological activities of CCK and gastrin, antagonists also tend to have affinity for both receptors. In a practical sense, however, there is enough selectivity to the different receptors that greater activity against specific CCK- or gastrin-related disorders can often also be identified.

30

Selective CCK antagonists are themselves useful in treating CCK-related disorders of the appetite regulatory systems of animals as well as in potentiating and prolonging opiate-mediated analgesia, thus having utility in the treatment of pain [see P. L. Faris et al., *Science* 226, 1215 (1984)], while selective gastrin antagonists are useful in the modulation of CNS behavior, as a palliative for gastrointestinal neoplasms, and in the treatment and prevention of gastrin-related disorders of the gastrointestinal system in humans and animals, such as peptic ulcers, Zollinger-Ellison syndrome, antral G cell hyperplasia and other conditions in which reduced gastrin activity is of therapeutic value. See e.g. U.S. Patent 4,820,834.

35

Applicants have made the unexpected discovery that CCK antagonists of Formula I are useful anxiolytic agents particularly in the treatment of panic disorder. As such, a new utility has been discovered for these CCK antagonists.

40

Since CCK and gastrin also have trophic effects on certain tumors [K. Okyama, *Hokkaido J. Med. Sci.*, 60, 206-216 (1985)], antagonists of CCK and gastrin are useful in treating these tumors [see, R.D. Beauchamp et al., *Ann. Surg.*, 202, 303 (1985)].

45

Four distinct chemical classes of CCK-receptor antagonists have been reported [R. Freidinger, *Med. Res. Rev.* 9, 271 (1989)]. The first class comprises derivatives of cyclic nucleotides, of which dibutyryl cyclic GMP has been shown to be the most potent by detailed structure-function studies (see, N. Barlas et al., *Am. J. Physiol.*, 242, G 161 (1982) and P. Robberecht et al., *Mol., Pharmacol.*, 17, 268 (1980)).

50

The second class comprises peptide antagonists which are C-terminal fragments and analogs of CCK, of which both shorter (Boc-Met-Asp-Phe-NH₂, Met-Asp-Phe-NH₂), and longer (Cbz-Tyr(SO₃H)-Met-Gly-Trp-Met-Asp-NH₂) C-terminal fragments of CCK can function as CCK antagonists, according to recent structure-function studies (see, R. T. Jensen et al., *Biochem. Biophys. Acta.*, 757, 250 (1983), and M. Spanarkel et al., *J. Biol.*

Chem., 258, 6746 (1983)). The latter compound was recently reported to be a partial agonist [see, J. M. Howard et al., Gastroenterology 86(5) Part 2, 1118 (1984)].

Then, the third class of CCK-receptor antagonists comprises the amino acid derivatives : proglumide, a derivative of glutamic acid, and the N-acyl tryptophans including para-chlorobenzoyl-L-tryptophan (benzotrypt), [see, W. F. Hahne et al., Proc. Natl. Acad. Sci. U.S.A., 78, 6304 (1981); R. T. Jensen et al., Biochem. Biophys. Acta., 761, 269 (1983)]. All of these compounds, however, are relatively weak antagonists of CCK (IC₅₀ : generally 10⁻⁴M (although more potent analogs of proglumide have been recently reported in F. Makovec et al., Arzneim-Forsch Drug Res., 35 (II), 1048 (1985) and in German Patent Application DE 3522506A1), but down to 10⁻⁶M in the case of peptides), and the peptide CCK-antagonists have substantial stability and absorption problems.

10 In addition, a fourth class consists of improved CCK-antagonists comprising a nonpeptide of novel structure from fermentation sources [R. S. L. Chang et al., Science, 230, 177-179 (1985)] and 3-substituted benzodiazepines based on this structure [published European Patent Applications 167 919, 167 920 and 169 392, B. E. Evans et al., Proc. Natl. Acad. Sci. U.S.A., 83, p. 4918-4922 (1986) and R.S.L. Chang et al, Ibid., p. 4923-4926] have also been reported.

15 No really effective receptor antagonists of the In vivo effects of gastrin have been reported (J. S. Morley, Gut Pept. Ulcer Proc., Hiroshima Symp. 2nd, 1983, p. 1), and very weak In vitro antagonists, such as proglumide and certain peptides have been described [(J. Martinez, J. Med. Chem. 27, 1597 (1984)]. Recently, however, 20 pseudopeptide analogs of tetragastrin have been reported to be more effective gastrin antagonists than previous agents [J. Martinez et al., J. Med. Chem., 28, 1874-1879 (1985)].

25 The benzodiazepine (BZD) structure class, which has been widely exploited as therapeutic agents, especially as central nervous system (CNS) drugs, such as anxiolytics, and which exhibits strong binding to "benzodiazepine receptors" in vitro, has not in the past been reported to bind to CCK or gastrin receptors. Benzodiazepines have been shown to antagonize CCK-induced activation of rat hippocampal neurones but 30 this effect is mediated by the benzodiazepine receptor, not the CCK receptor [see J. Bradwejn et al., Nature, 312, 363 (1984)]. Benzodiazepines unsubstituted at the 3-position of the seven membered ring also have been shown to antagonize the effects of CCK-4 (a CCK analog) [see De-Montigny, C. Arch. Gen. Psychiatry 46, 511 (1989)]. Of the reported BZD's, additionally, the large majority do not contain substituents attached to the 3-position of the seven membered ring, as it is well known in the art that 3-substituents result in decreasing benzodiazepine receptor affinity and decreasing anxiolytic activity, especially as these substituents increase in size.

35 Contrary to these findings, applicants have discovered a class of benzodiazepines with 3-substituents having high CCK receptor affinity and low benzodiazepine receptor affinity, which are useful anxiolytic agents, particularly in the treatment of panic disorder, panic syndrome and similar anxiety states. The compounds of the invention are useful in treating anxiety states involving apprehension, uncertainty and fear without apparent stimulus.

40 It is, therefore, an object of this invention to identify substances which more effectively antagonize or inhibit the function of cholecystokinins and gastrin in psychiatric disease states involving anxiety or panic in mammals, especially in humans. It is another object of this invention to develop a method of antagonizing the functions of cholecystokinin and/or gastrin in panic disorder or other neurological disorders involving anxiety or panic in mammals. It is also an object of this invention to develop a method of preventing or treating neurochemical disorders involving panic disorder, panic syndrome and similar anxiety states.

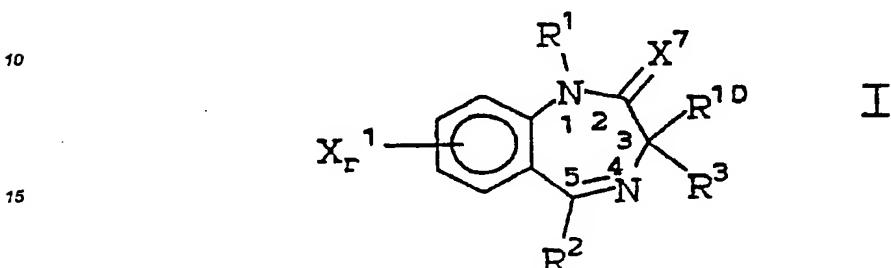
45 The substituted benzodiazepines of the present invention are also useful for directly inducing analgesia, which includes opiate and non-opiate mediated analgesia. Furthermore, the compounds of the present invention are useful as anesthetic agents involving the loss of pain sensations. It is therefore another object of the present invention to identify substances which more effectively antagonize or inhibit the function of CCK or gastrin for the purpose of effecting analgesia, anesthesia, or loss of pain sensation. Yet another object of the present invention is to develop methods of antagonizing or inhibiting the functions of CCK or gastrin for the purpose of effecting analgesia, anesthesia or loss of pain sensation.

50 SUMMARY OF THE INVENTION

55 It has now been found that compounds of Formula I are antagonists of gastrin and cholecystokinin (CCK) and bind to the gastrin and CCK receptors. Pharmaceutical compositions containing effective amounts of these compounds are useful in the treatment and prevention of CCK-related neurochemical disorders such as panic disorder, panic syndrome and similar anxiety states, and are also useful in effecting analgesia. Methods of treating such disorders and for effecting analgesia are also disclosed.

DETAILED DESCRIPTION OF THE INVENTION

5 The compounds of formula I are useful in a method of antagonizing the binding of cholecystokinin to cholecystokinin receptors or antagonizing the binding of gastrin to gastrin receptors, for treating panic disorder and for inducing analgesia, which comprises contacting said cholecystokinin receptors or said gastrin receptors, respectively, with a compound represented by the formula :



20 wherein :

R¹ is H, C₁₋₆ linear or branched alkyl, -X¹²-cycloalkyl, -X¹²COOR⁶,

25 -X¹²CONR⁴R⁵, X¹²N(R⁴)₂, or -X¹²OR⁶;

30 R² is substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, carboxyl, nitro or -CF₃); -X¹²COOR⁶; 2-, 3-, 4-pyridyl;

35 R³ is $\begin{array}{c} \text{H} \quad \text{O} \\ || \quad || \\ \text{N}-\text{CR}^7 \end{array}$ or $\begin{array}{c} \text{H} \quad \text{O} \quad \text{H} \\ || \quad || \quad | \\ \text{N}-\text{C}-\text{NR}^7 \end{array}$ or $\begin{array}{c} \text{O} \\ || \\ \text{-CR}^7 \end{array}$ or $\begin{array}{c} \text{H} \quad \text{O} \\ || \quad || \\ \text{N}-\text{CCH}_2\text{R}^7 \end{array}$;

40 R⁴ and R⁵ are independently R⁶ or in combination with the N of the NR⁴R⁵ group form an unsubstituted or mono- or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH₃ and the substituent(s) is/are independently selected from C₁₋₄ alkyl;

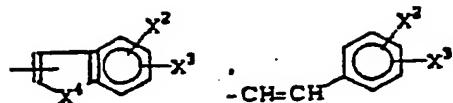
45 R⁶ is H, C₁₋₆ straight or branched-chain alkyl or cycloalkyl;

R⁷ is α - or β -naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, -NO₂, -OH, -NR⁴R⁵, loweralkyl, CF₃, CN, COOR⁶, X¹²COOR⁶, X¹²OR⁶, or loweralkoxy) 2-, 3-, 4-pyridyl,

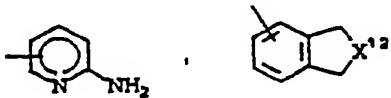
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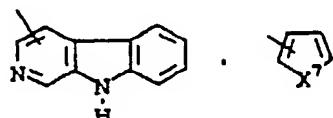
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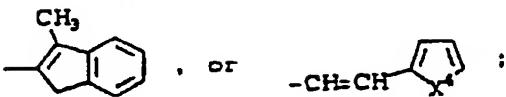


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R^{10} is H or $-OH$ where R^3 is CR^7 , otherwise it is H;
 r is 1 or 2;

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X^1 is H, $-NO_2$, CF_3 , loweralkyl or halo;
 X^2 and X^3 are independently H, $-NO_2$, OH, halo, loweralkyl, loweralkoxy, $X^{12}COOR^6$, $COOR^6$, or
 $OX^{12}COOR^6$;

X^4 is O, or NR^8 ;

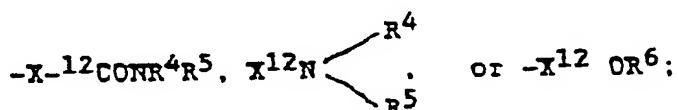
X^7 is O;

X^{12} is C_{1-6} linear or branched chain alkyl, or the pharmaceutically acceptable salt thereof.

Pharmaceutical compositions comprising any of these compounds are also encompassed within the present invention.

A first embodiment of the present invention are compounds of formula I, wherein
 R^1 is H, C_1-C_4 linear or branched chain alkyl, $-X^{12}-cycloalkyl$, $-X^{12}COOR^6$,

45

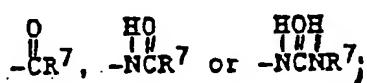


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R^2 is substituted or unsubstituted phenyl (wherein the substituent may be 1 or 2 of halo, loweralkyl, nitro, $-CF_3$), 2-,3-,4-pyridyl, or $X^{12}COOR^6$;
 R^3 is



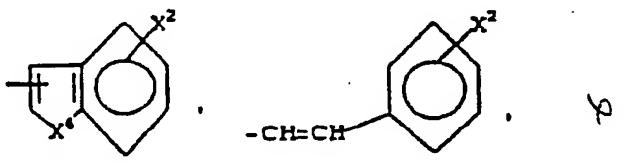
R^4 and R^5 are independently R^8 or in combination with the N of the NR^4R^5 group form an unsubstituted

or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH₃ and the substituent(s) is/are independently selected from C₁₋₄ alkyl;

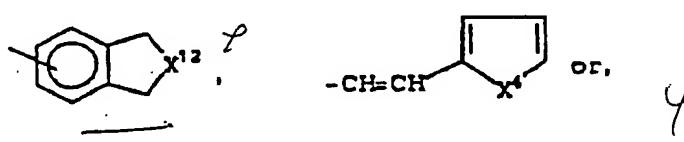
5 R⁶ is H, C₁-C₃ straight chain alkyl;

R⁷ is α - or β -naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, -NO₂, NH₂, methyl, ethyl, CF₃, CN, COOH, X¹²OR⁶, or lower alkoxy), 2-, 3-, 4-pyridyl,

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R¹⁰ is H, or OH when R³ is CR⁷, otherwise R¹⁰ is H;
 .x is 1 or 2;

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X¹ is H, -NO₂, CF₃, loweralkyl or halo;
 X² is H, -NO₂, halo, OH, loweralkoxy, loweralkyl,
 X¹²COOH, or OCH₂COOH;

X⁴ is O, NH, NCH₃, NX¹²COOH;

X⁷ is O;

X¹² is C₁₋₅ linear alkyl;

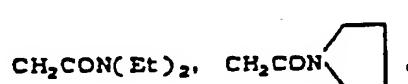
or pharmaceutically acceptable salt thereof.

A second embodiment has the further limitation that, is formula I,

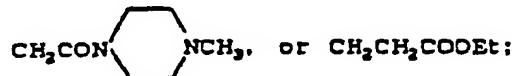
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R¹ is H, CH₃, CH₂CH₃, CH₂CH(CH₃)₂, CH₂-,
 -CH₂CH₂OH, CH₂COOH, CH₂COOEt,

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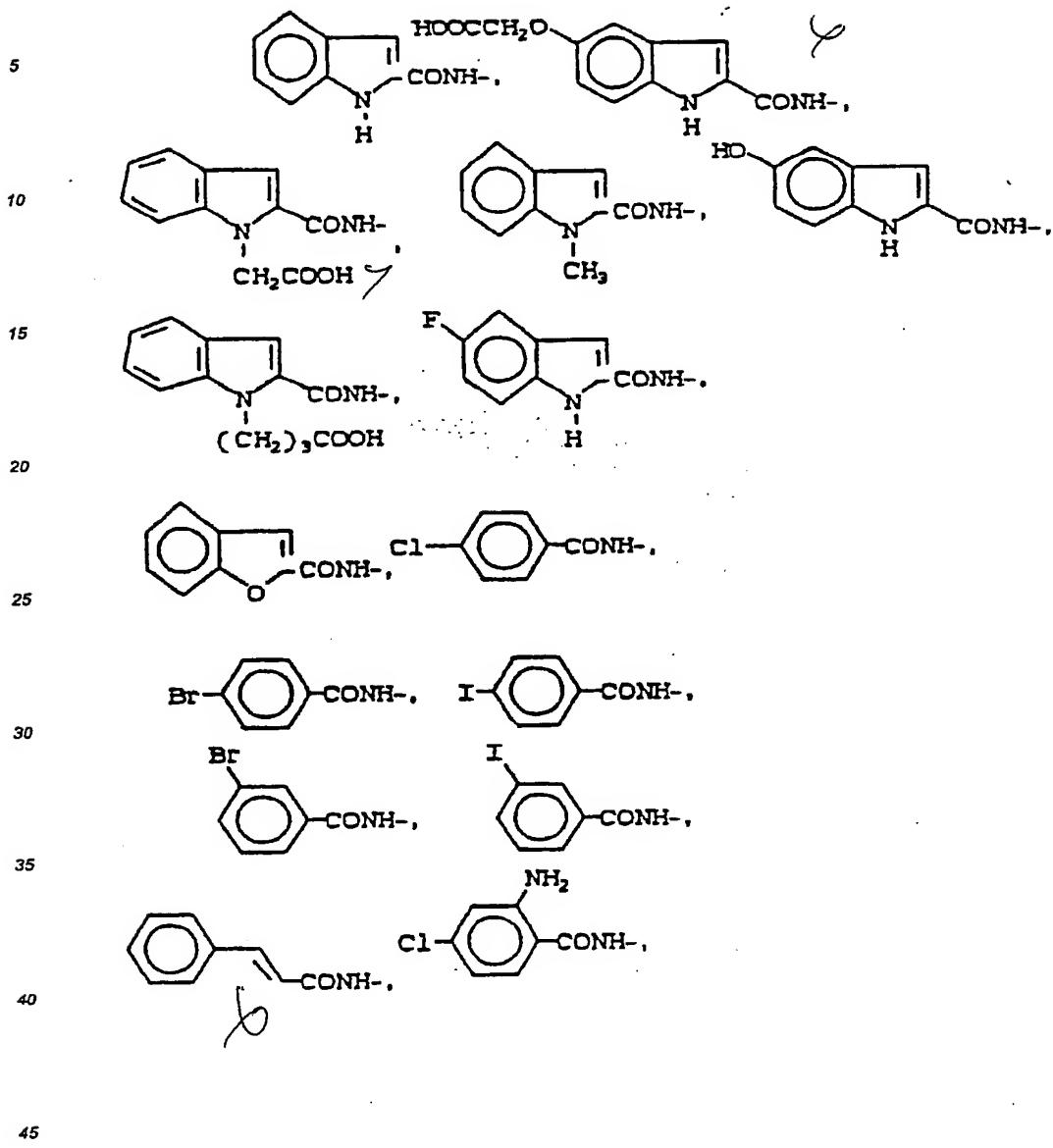


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R² is phenyl, 2-F-phenyl, 4-CH₃-phenyl, 2-, 3-, or 4-pyridyl;

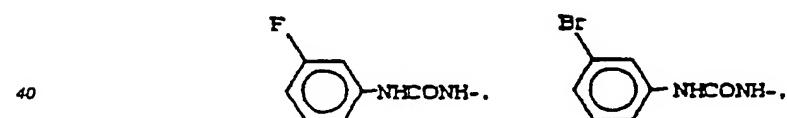
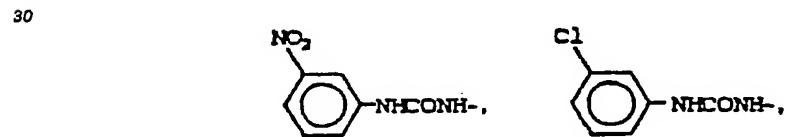
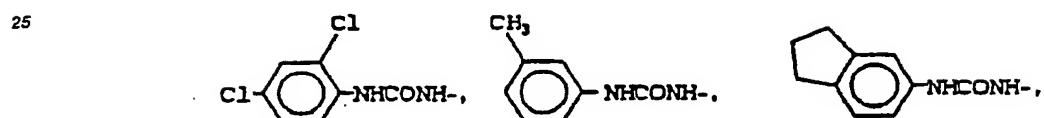
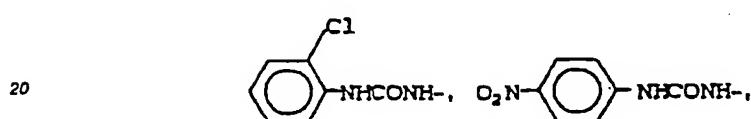
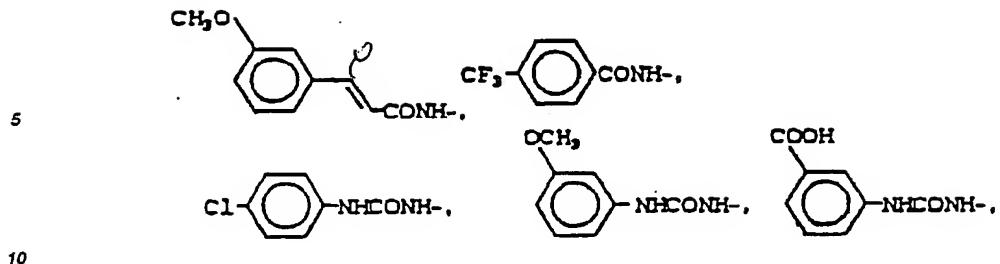
R³ Is



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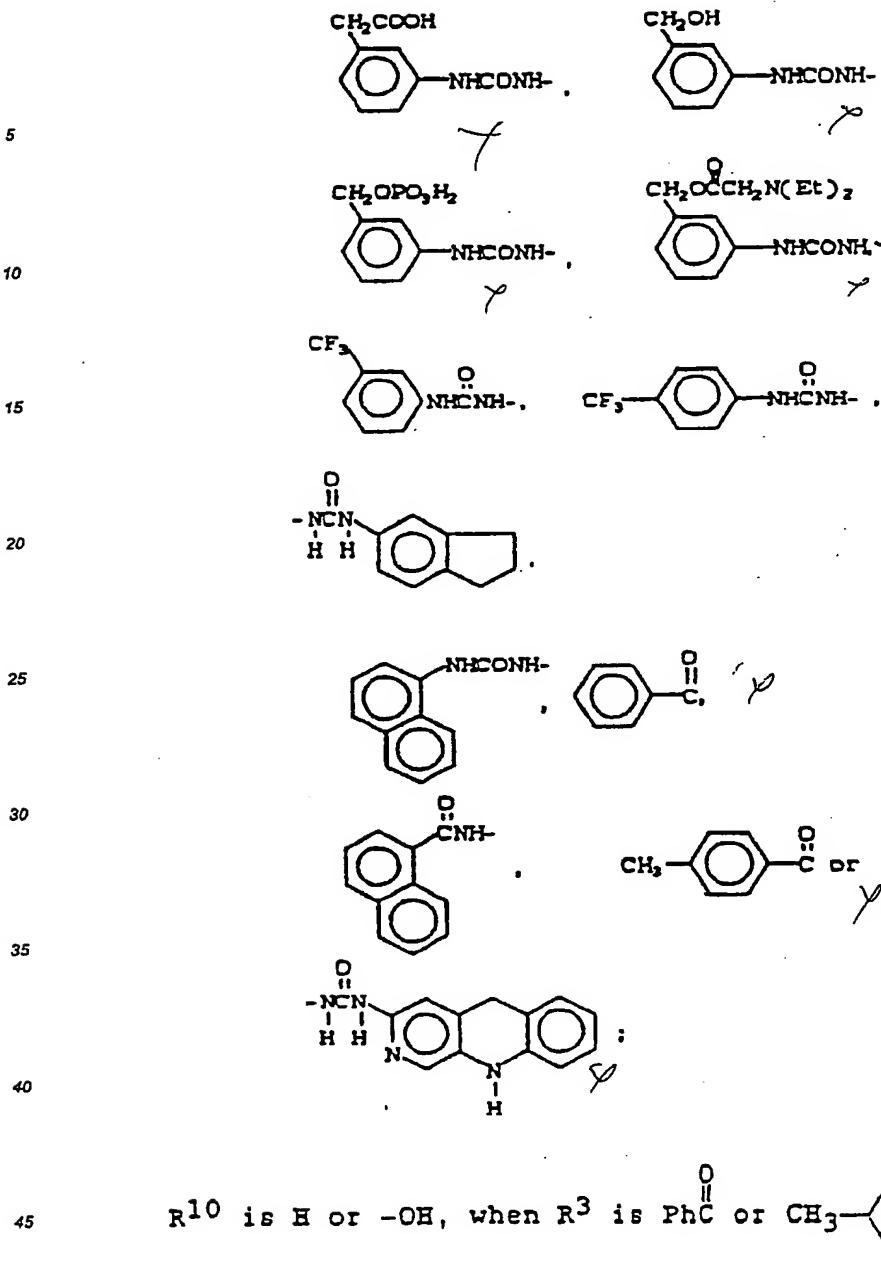
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otherwise $R^{10}=H$;
 50 X^1 is H , Cl ; or $-CH_3$;

X^7 is O ;
or a pharmaceutically acceptable salt thereof.

Preferred compounds include the following :

55 3-N-(2,3-Dihydro-1-methyl-2-oxo-5-(p-tolyl)-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,
 3-N-(2,3-Dihydro-1,9-dimethyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,
 3-N-(2,3-Dihydro-1,8-dimethyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,
 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-3-phenyl-2-propenamide,
 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(2-chlorophenyl)-urea,

1,3-Dihydro-3-(5-carboxymethoxyindole-2-carbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, 1,3-Dihydro-3-(5-hydroxyindole-2-carbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, 1,3-Dihydro-3-(5-(2-Fluorophenyl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-4-(trifluoromethyl)-benzamide,

5 3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one, 3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one, 3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, 3-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-2-amino-4-chlorobenzamide, 4-Bromo-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-benzamide,

10 1,3-Dihydro-5-(2-fluorophenyl)-1-methyl-3(RS)-[2'-(1'-methylindole)carbonylamino]-2H-1,4-benzodiazepin-2-one, (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methoxyphenyl)-urea, 1,3-dihydro-1-methyl-3(RS)-[2-(1-methylindole)-carbonylamino]-5-phenyl-2H-1,4-benzodiazepin-2-one, Carboxymethyl-1,3-dihydro-3(RS)-(2-indolecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one,

15 3(S)-(+)-1,3-Dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one, 3-[[((3-Methoxyphenyl)amino)carbonyl]amino]-N,N-diethyl-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepi- n-1-acetamide,

20 1-(((3-(((4-Chlorophenyl)amino)carbonyl)amino)-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-acetyl)pyrrolidine,

25 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea, 3-[[((2-Chlorophenyl)amino)carbonyl]amino]-N,N-diethyl-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepi- 1-acetamide,

30 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-bromophenyl)-urea, (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(4-methylphenyl)-urea, (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxymethylphenyl)-urea,

35 (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(5-indanyl)-urea, N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxymethylphenyl)urea, (R)-N-(6-Amino-3-pyridinyl)-N'-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl) urea, or N-(2,3-Dihydro-1-(2-hydroxyethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or pharmaceutically acceptable salt thereof.

As used herein, the definition of each substituent e.g., R⁷, loweralkyl, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

As used herein, halo is F, Cl, Br or I; alkyl and loweralkyl are each, unless otherwise indicated, 1-7 carbon straight or branched chain saturated alkyl having one or sometimes two hydrogens abstracted, and includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and t-butyl, pentyl, hexyl, and heptyl; in loweralkoxy and loweralkylthio, the alkyl portion is loweralkyl as previously defined; cycloloweralkyl is cycloalkyl of 3-7 carbons; loweralkenyl is 1-5 carbon straight or branched chain alkenyl; acyl is formyl, acetyl, propionyl, benzoyl or butyryl; loweralkynyl is 1-5 carbon straight or branched chain alkylnyl; Et is ethyl.

The pharmaceutically acceptable salts of the compounds of Formulas I include the conventional non-toxic salts or the quarternary ammonium salts of the compounds of Formula I formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acids of Formula I are also readily prepared by conventional procedures such as treating an acid of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

The compounds of Formula I antagonize CCK and/or gastrin and are useful as pharmaceutical agents for mammals, especially for humans, in the treatment or prevention of neurological disorders involving anxiety and other panic type states wherein CCK and/or gastrin is involved. Examples of such disorders include panic disorder, panic syndrome, anticipatory anxiety, phobic anxiety, panic anxiety, chronic anxiety, phobic anxiety and

endogenous anxiety. The compounds of formula I are also useful for directly inducing analgesia, opiate or non-opiate mediated, as well as anesthesia or loss of the sensation of pain.

The present invention also encompasses a pharmaceutical composition useful in the treatment of panic disorder or other neurological disorders involving anxiety, comprising an effective amount of a CCK and/or gastrin antagonist of formula I, with or without pharmaceutically-acceptable carriers or diluents. In addition, the present invention encompasses a pharmaceutical composition useful for directly inducing analgesia, anesthesia or loss of the sensation of pain.

The compounds of Formula I thereof, may be administered to a human subject either alone or, preferably, in combination with pharmaceutically-acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including intravenous, intramuscular, intraperitoneal, subcutaneous and topical administration.

For oral use of an antagonist of CCK, according to this invention, the selected compounds may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

When a compound according to Formula I is used as an antagonist of CCK or gastrin in a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms. However, in most instances, an effective daily dosage will be in the range of from about 0.05 µg/kg to about 5 mg/kg of body weight, and preferably, of from about 0.5 µg/kg to about 0.5 mg/kg of body weight, administered in single or divided doses. In some cases, however, it may be necessary to use dosages outside these limits.

In the effective treatment of panic syndrome, panic disorder and the like, about 0.005 µg/kg to about 0.5 mg/kg of CCK antagonist is administered orally (p.o.), divided into two doses per day (b.i.d.). Other routes of administration are also suitable.

For directly inducing analgesia, anesthesia or loss of pain sensation, the effective dosage ranges from about 100 ng/kg to about 1 mg/kg by intraperitoneal administration. Oral administration is an alternative route, as well as others.

Because these compounds antagonize the function of CCK in animals, they may also be used as feed additives to increase the food intake of animals in daily dosage of approximately 0.005 to 100 µg/kg of body weight.

The compounds of Formula I are prepared according to the schemes and descriptions of U.S. Patent 4,820,834 herein incorporated by reference for these purposes. One preferred synthetic scheme is Scheme IVa involving nitrosation, reduction and acylation, according to U.S. Patent 4,820,834. See also Examples 1-5 below.

MATERIALS AND METHODS

45 1. Anxiolytic activity of the compounds of Formula I :

The black/white exploration test [Crawley et al. *Pharmacology, Biochemistry and Behav.* 13, 167 (1980)] is a simple animal model of anxiety. Rodents placed in a two compartment box which consists of a brightly lit, white painted side and a dimly lit, black painted side, display a marked preference for the black side of the apparatus. This behavior is caused by the aversive properties of the brightly lit, white painted section. Classical anxiolytic drugs [such as diazepam, see Crawley, *supra*] and novel anxiolytic drugs [such as 5HT₃ antagonists, see Jones et al. *Br. J. Pharm.* 93, 985 (1988)] decrease the preference of the animal for the black dimly lit side of the apparatus.

A. Naive male DBA2 mice (25-30) were housed on a reversed light/dark cycle and tested during the dark phase of the cycle under dim red light. The apparatus consisted of an open topped box (40cm long X 27 cm wide X 27 cm high) divided into a small area (2/5) and a large area (3/5) by a partition that extended 20 cm above the walls. There was a 7.5 X 7.5 cm opening in the partition at floor level. The small compartment was painted black and the large compartment white. The floor of each compartment was marked into 9 cm squares.

The white compartment was illuminated by a 100 W tungsten bulb 17 cm above the box and the black compartment by a similarly placed 60 W red bulb.

5 Animals that had been injected with drug or vehicle were placed individually into the centre of the white area and their behavior observed during a 5 minute period by remote video recording. Four behavioral parameters were recorded every minute : the number of exploratory rears in the white and black sections, the number of line crossings in the black and white sections, the number of transitions between the two sections and the time spent in the black and white sections. Animals were tested in treatment groups of 8-10 and vehicle controls were run on each test day. Data were analysed by ANOVA and Dunnett's test.

10 In one series of tests, the following compounds were employed :
 Compound A : 3(S)-(-)-1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, an effective antagonist of CCK-A receptors ;
 Compound B : (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methyl-phenyl)urea, an effective antagonist of CCK-B receptors.

15 Vehicle treated animals displayed a marked preference for activity in the black side of the test arena, probably induced by the aversive properties of the brightly lit, white painted section. Compound A at doses of 0.05, 0.5, 5.0 and 500 μ g/kg significantly decreased the preference for rearing in the black side. Similarly, 0.5, 5.0 and 500 μ g/kg of Compound A abolished the preference for locomotion (line crossings) in the black side. The difference in time spent in the black and white side was abolished by 5.0 and 500 μ g/kg of Compound A. Compound B at a dose of 0.05 μ g/kg abolished the preference for rearing in the black side and a dose of 0.005 μ g/kg decreased the difference in time spent in the black and white side.

20 These results demonstrate that CCK antagonists have anxiolytic properties in mice. The active dose range for Compound B (0.005-0.05 μ g/kg) was lower than that for Compound A (0.05-5.0 μ g/kg), suggesting that the response may be mediated by CCK-B receptors. This is consistent with studies in humans in which CCK-4 (which is a preferential CCK-B receptor agonist) was reported to induce panic, whereas CCK-8 (which is equipotent as an agonist at CCK-A and CCK-B receptors) induced gastrointestinal effects but not panic symptoms.

25 Therefore, compounds A and B are clinically useful in the treatment of anxiety.

26 B. The effects of CCK-8 and compound A on the exploratory behavior of the rat were examined in automated activity cages and by direct observation. It is known that exogenous CCK-8 decreases exploratory behavior in rats in a novel environment by accelerating the process of habituation. [See Crawley, *Pharm.*

30 *Biochem & Behav.* 20, 23-27 (1984).]

31 Expt 1. Male Sprague Dawley rats were injected (1.p.) with CCK-8 and immediately placed in automated activity cages. Activity was measured for 30 minutes post injection. CCK-8 (0.5-16 μ g/kg) dose-dependently decreased locomotor activity $F(6,87) = 3.21$ ($p < 0.01$). These results confirm previous reports that CCK decreases locomotor activity in a novel environment.

35 Expt 2. Male SD rats were injected (s.c.) with the CCK antagonist compound A (0.0001-10mg/kg) and immediately placed in the automated activity cages. Compound A delayed habituation and prolonged the period of exploratory activity of the rats $F(6,124) = 2.54$, $p < 0.05$. The drug effects were most pronounced at 25 minutes where 0.1 mg/kg induced levels of activity significantly above controls $F(6,124) = 3.18$, $p < 0.01$. The dose response curve was bell-shaped with higher and lower doses having no significant effect on activity at the time point. As the anxiolytic drug chlordiazepoxide also increases spontaneous locomotor activity in rats in a novel environment [(McElroy et al. *Psychopharm.* 85 : 224-226 (1985)] these findings are consistent with an anxiolytic action of Compound A useful in the treatment of panic disorder.

40 Expt 3. In order to assess further the effect of Compound A on exploration in a novel environment, the motoric behaviors of rats placed in a perspex cage was recorded by direct observation for a 15 minute period 15 minutes after treatment with Compound A.

45 Experimenters (unaware of the treatments the animals had received) recorded the frequency and duration of rearing, sniffing, grooming and cage crossing using a keypad interfaced to a BBC microcomputer.
 Sniffing, ($F(3,43) = 3.96$, $P < 0.01$) rearing ($F(3,43) = 4.77$, $P < 0.01$) and cage crossing ($F(3,43) = 3.79$, $P < 0.05$) were all significantly increased by 0.1 mg/kg of Compound A. These results are consistent with the data from the automatic activity measures (see Experiment 2) and further support the utility of compound A in the treatment of panic disorder.

2. CCK Receptor Binding (Pancreas)

50 55 CCK-33 was radiolabeled with 125 I-Bolton Hunter reagent (2000 Ci/mmole) as described by Sankara et al. (*J. Biol. Chem.* 254 : 9349-9351, 1979). Receptor binding was performed according to Innis and Snyder (*Proc. Natl. Acad. Sci.* 77, 6917-6921, 1980) with the minor modification of adding the additional protease inhibitors, phenylmethane sulfonyl fluoride and o-phenanthroline. The latter two compounds have no effect on the 125 I-

CCK receptor binding assay.

Male Sprague-Dawley rats (200-350g) were sacrificed by decapitation. The whole pancreas was dissected free of fat tissue and was homogenized in 20 volumes of ice-cold 50 mM Tris HCl (pH 7.7 at 25°C) with a Brinkmann Polytron PT 10. The homogenates were centrifuged at 48,000 g for 10 min. Pellets were resuspended in Tris Buffer, centrifuged as above and resuspended in 200 volumes of binding assay buffer (50 mM Tris HCl, pH 7.7 at 25°C, 5 mM dithiothreitol, 0.1 mM bacitracin, 1.2 mM phenylmethylene sulfonyl fluoride and 0.5 mM o-phenanthroline). For the binding assay, 25 µl of buffer (for total binding) or unlabeled CCK-8 sulfate to give a final concentration of 1 µM (for nonspecific binding) or the compounds of Formula I (for determination of inhibition of ¹²⁵I-CCK binding) and 25 µl of ¹²⁵I-CCK-33 (30,000-40,000 cpm) were added to 450 µl of the membrane suspensions in microfuge tubes. All assays were run in duplicate or triplicate. The reaction mixtures were incubated at 37°C for 30 minutes and centrifuged in a Beckman Microfuge (4 minutes) immediately after adding 1 ml of ice-cold incubation buffer. The supernatant was aspirated and discarded, pellets were counted with a Beckman gamma 5000. For Scatchard analysis (Ann. N.Y. Acad. Sci. 51 : 660, 1949), ¹²⁵I-CCK-33 was progressively diluted with increasing concentrations of CCK-33.

3. CCK Receptor Binding (Brain)

CCK-33 was radiolabeled and the binding was performed according to the description for the pancreas method with modifications according to Saito et al., J. Neurochem. 37 : 483-490, 1981.

Male Hartley guinea pigs (300-500g) were sacrificed by decapitation and the brains were removed and placed in ice-cold 50 mM Tris HCl plus 7.58 g/l Trizma-7.4 (pH 7.4 at 25°C). Cerebral cortex was dissected and used as a receptor source. Each gram of fresh guinea pig brain tissue was homogenized in 10 ml of Tris/Trizma buffer with a Brinkman polytron PT-10. The homogenates were centrifuged at 42,000 g for 15 minutes. Pellets were resuspended in Tris Buffer, centrifuged as above and resuspended in 200 volumes of binding assay buffer (10 mM N-2-hydroxyethyl-piperazine-N'-2-ethane sulfonic acid (HEPES), 5 mM MgCl₂, 0.25 mg/ml bacitracin, 1 mM ethylene glycol-bis-(β-aminoethyl-ether-N,N'-tetraacetic acid) (EGTA), and 0.4% bovine serum albumin (BSA)). For the binding assay, 25 µl of buffer (for total binding) or unlabeled CCK-8 sulfate to give a final concentration of 1 µM (for nonspecific binding) or the compounds of Formula I (for determination of inhibition of ¹²⁵I-CCK binding) and 25 µl of ¹²⁵I-CCK-33 (30,000-40,000 cpm) were added to 450 µl of the membrane suspensions in microfuge tubes. All assays were run in duplicate or triplicate. The reaction mixtures were incubated at 25°C for 2 hours and centrifuged in a Beckman Microfuge (4 minutes) immediately after adding 1 ml of ice-cold incubation buffer. The supernatant was aspirated and discarded, pellets were counted with a Beckman gamma 5000.

The compounds of Formula I can be determined to be competitive antagonists of CCK according to the following assays.

4. Isolated guinea pig gall bladder

Male Hartley guinea pigs (400-600 g) are sacrificed by decapitation. The whole gall bladder is dissected free from adjacent tissues and cut into two equal halves. The gall bladder strips are suspended along the axis of the bile duct in a 5 ml organ bath under 1 g tension. The organ bath contains a Kreb's bicarbonate solution (NaCl 118 mM, KCl 4.75 mM, CaCl 2.54 mM, KH₂PO₄ 1.19 mM, Mg SO₄ 1.2 mM, NaHCO₃ 25 mM and dextrose 11 mM) maintained at 32°C and bubbled with 95% O₂ and 5% CO₂. Isometric contractions are recorded using Statham (60 g ; 0.12 mm) strain gauges and a Hewlett-Packard (77588) recorder. The tissues are washed every 10 minutes for 1 hour to obtain equilibrium prior to the beginning of the study. CCK-8 is added cumulatively to the baths and EC₅₀'s determined using regression analysis. After washout (every 10 minutes for 1 hour), the compound of Formula I is added at least 5 minutes before the addition of CCK-8 and the EC₅₀ of CCK-8 in the presence of the compound of Formula I similarly determined.

5. Isolated longitudinal muscle of guinea pig ileum

Longitudinal muscle strips with attached nerve plexus are prepared as described in Brit. J. Pharmac. 23 : 356-363, 1964 ; J. Physiol. 194 : 13-33, 1969. Male Hartley guinea pigs are decapitated and the ileum removed (10 cm of the terminal ileum is discarded and the adjacent 20 cm piece used). A piece (10 cm) of the ileum is stretched on a glass pipette. Using a cotton applicator to stroke tangentially away from the mesentery attachment at one end, the longitudinal muscle is separated from the underlying circular muscle. The longitudinal muscle is then tied to a thread and by gently pulling, stripped away from the entire muscle. A piece of approximately 2 cm is suspended in 5 ml organ bath containing Krebs solution and bubbled with 95% O₂ and 5% CO₂ at 37°C

under 0.5 g tension. CCK-8 is added cumulatively to the baths and EC₅₀ values in the presence and absence of compounds of Formula I determined as described in the gall bladder protocol (above).

6. Gastrin Antagonism

5

Gastrin antagonist activity of compounds of Formula I is determined using the following assay.

A. Gastrin Receptor Binding in Guinea Pig Gastric Glands

10

Preparation of guinea pig gastric mucosal glands

15

Guinea pig gastric mucosal glands were prepared by the procedure of Berglingh and Obrink *Acta Physiol. Scand.* 96 : 150 (1976) with a slight modification according to Praissman *et al.* *C. J. Receptor Res.* 3 : (1983). Gastric mucosa from guinea pigs (300-500 g body weight, male Hartley) were washed thoroughly and minced with fine scissors in standard buffer consisting of the following : 130 mM NaCl, 12 mM NaHCO₃, 3 mM NaH₂PO₄, 3 mM Na₂HPO₄, 3 mM K₂HPO₄, 2 mM MgSO₄, 1 mM CaCl₂, 5 mM glucose and 4 mM L-glutamine, 25 mM HEPES at pH 7.4. The minced tissues were washed and then incubated in a 37°C shaker bath for 40 minutes with the buffer containing 0.1% collagenase and 0.1% BSA and bubbled with 95% O₂ and 5% CO₂. The tissues were passed twice through a 5 ml glass syringe to liberate the gastric glands, and then filtered through 200 mesh nylon. The filtered glands were centrifuged at 270 g for 5 minutes and washed twice by resuspension and centrifugation.

20

B. Binding studies

25

The washed guinea pig gastric glands prepared as above were resuspended in 25 ml of standard buffer containing 0.25 mg/ml of bacitracin. For binding studies, to 220 µl of gastric glands in triplicate tubes, 10 µl of buffer (for total binding) or gastrin (1 µM final concentration, for nonspecific binding) or test compound and 10 µl of ¹²⁵I-gastrin (NEN, 2200 Ci/mmol, 25 pM final) or ³H-pentagastrin (NEN 22 Ci/mmol, 1 nM final) were added. The tubes were aerated with 95% O₂ and 5% CO₂ and capped. The reaction mixtures after incubation at 25°C for 30 minutes were filtered under reduced pressure on glass G/F B filters (Whatman) and immediately washed further with 4 x 4 ml of standard buffer containing 0.1% BSA. The radioactivity on the filters was measured using a Beckman gamma 5500 for ¹²⁵I-gastrin or liquid scintillation counting for ³H-pentagastrin.

30

In vitro Results

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Effect of the Compounds of Formula I on ¹²⁵I-CCK-33 receptor binding

The preferred compounds of Formula I are those which inhibited specific ¹²⁵I-CCK-33 binding in a concentration dependent manner.

40

Scatchard analysis of specific ¹²⁵I-CCK-33 receptor binding in the absence and presence of the compounds of Formula I indicated the compound of Formula I competitively inhibited specific ¹²⁵I-CCK-33 receptor binding since it increased the K_D (dissociation constant) without affecting the B_{max} (maximum receptor number). A K_i value (dissociation constant of inhibitor) of the compounds of Formula I was estimated.

The data of Table I were obtained for compounds of Formula I.

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50

55

TABLE I
CCK RECEPTOR BINDING RESULTS

		<u>IC₅₀ (μM)</u>		
		<u>125I-CCK</u>	<u>125I-CCK</u>	<u>125I-Gastrin</u>
		<u>Pancreas</u>	<u>Brain</u>	<u>Gastric Glands</u>
10	Compound of EX#	125I-CCK	125I-CCK	125I-Gastrin
	5	0.28	0.002	0.0011
15	6	0.00013	0.129	0.070
	7	0.0001	0.23	0.24
20	9	0.049	0.0039	0.009
	11	0.0041	>0.1	0.092
25	16	0.00008	0.27	0.17
	17	0.0068	0.69	0.66
30	20	0.0024	0.160	0.24
	21	0.014	0.071	6.4
35	22	0.0044	0.021	1.3
	23	2.7	0.011	0.4
40	24	0.00037	0.2	0.16
	25	0.49	0.0011	0.00067
45	26	0.075	0.0018	0.0019
	27	0.0033	0.91	--
50	28	0.023	0.16	--
	29	0.069	0.012	0.0038

EXAMPLE 11,3-Dihydro-1-methyl-3-oximino-5-phenyl(-2H-1,4-benzodiazepin-2-one

To a suspension of potassium *tert*-butoxide (24.9 g, 222 mmole) in 600 ml of dry tetrahydrofuran was added 200 ml of dry *tert*-butylalcohol at -20°C under nitrogen. To this solution was then added via addition funnel 1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (25 g, 99.9 mmole) in 260 ml of tetrahydrofuran. The resulting wine colored solution was stirred for 2 hours at -20°C and treated with 17.4 ml (130 mmole) of isoamyl nitrite. The reaction mixture was warmed to 0°C over 15 minutes and quenched with the addition of 60 ml of cold water and 20 ml of glacial acetic acid. All solvents were removed under reduced pressure and the residue was partitioned between ethyl acetate (600 ml) and brine (100 ml). The phases were separated and the organic extracts were dried (Na₂SO₄) and concentrated. The resulting semi-solid was triturated with ether to give 21 g of off-white solid. m.p. 234-235°C ;

R_f=0.15 (ethyl acetate-hexane, 1 : 1) ; R_f=0.28 chloroform-ethanol, 95 : 5) ;
ir(KBr, partial) : 3300, 1650, 1595, 1320, 1205, 1030, 975 cm⁻¹.

MS (14 ev.) : 279 (M⁺), 262, 249, 236, 222.

¹HNMR (CDCl₃) : confirms structure assignment.

Elemental Analysis Calc'd for C₁₆H₁₃N₃O₂ :

C, 4.69 ; H, 68.81 ; N, 15.04.

Found : C, 4.62 ; H, 68.67 ; N, 15.08.

EXAMPLE 2X 3(R,S)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

5 A solution of 150 ml of methanol containing 5 g (17.9 mmole) of 1,3-dihydro-1-methyl-3-oximino-5-phenyl-1,4-benzodiazepin-2-one was treated with a slurry of active Raney-nickel catalyst¹ in ethanol (10 g wet weight). The resulting suspension was hydrogenated on a Parr apparatus at 60 psi and 23°C for 30 hours. The catalyst was removed by filtration and the filtrate was concentrated to afford the title compound in 95% yield.
 R_f =0.23 (chloroform-ethanol, 95 : 5), R_f =0.23 (chloroform-methanol-acetic acid-water, 90 : 10 : 1 : 1)

10 ¹H NMR ($CDCl_3$) : spectrum confirms structure assignment.

1 Raney-Nickel catalyst was prepared according to Fieser & Fieser, Reagents for Organic Synthesis, Vol. I, John Wiley & Sons, Inc., New York 1967, p. 729.

EXAMPLE 315 3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

20 3(S)-(-)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (595 mg, 2.24 mmole) was dissolved in CH_2Cl_2 (15 ml) and treated with 2-indolecarbonyl chloride (403 mg, 2.24 mmole) followed by triethylamine (227 mg, 2.24 mmole). The mixture was stirred at room temperature for 30 minutes and concentrated in vacuo. The residue was chromatographed on silica gel (5% Et_2O/CH_2Cl_2) and the combined product fractions evaporated to dryness in vacuo. Three times, Et_2O (15 ml) was added and evaporated in vacuo to give the title compound : (m.p 168° - 185°C).

25 TLC : Silica gel (6%, Et_2O/CH_2Cl_2), R_f = 0.23

NMR : Consistent with structure

HPLC : Greater than 99% pure.

M.S. : Molecular ion at m/e = 408

$[\alpha]D^{25} = -103^\circ$ (0.0078 g/ml CH_2Cl_2)

Anal. calc'd for $C_{25}H_{20}N_4O_2$:

30 C, 73.51 ; H, 4.94 ; N, 13.72 ;

Found : C, 73.38 ; H, 4.80 ; N, 13.66.

EXAMPLE 435 3(RS)-(Boc-L-tryptophanyl)amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (0.1 g, 0.4 mmol), BOC-L-tryptophan (0.12 g, 0.4 mmol), and DCC (0.4 ml of a 1 M solution in CH_2Cl_2 , 0.4 mmol) were combined in 2 ml of THF to which were added 2 ml of DMF and 2 ml of CH_2Cl_2 . The mixture was treated with triethylamine (0.11 ml), stoppered, and stirred at room temperature for four days. The mixture was treated with citric acid solution (10%, 3 ml) and CH_2Cl_2 (5 ml), shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 5 ml). The combined organic layers were washed with citric acid (10%, 2 x 5 ml), sodium bicarbonate (10%, 2 x 5 ml), and H_2O (10 ml), dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (1 : 1 (v/v) Et_2O/CH_2Cl_2) and the combined product fractions evaporated to dryness in vacuo. The residue was triturated with petroleum ether and the solid dried in vacuo at 70° : (m.p. 173-177°C (1)).

TLC : Single spot (R_f = 0.56, silica gel plate, 10% (v/v) CH_3OH in CH_2Cl_2).

NMR : The spectrum was consistent with the title structure and verified the presence of two diastereomers.

HPLC : Greater than 99.7% pure (36% and 63.7%).

50 MS (FAB) : a molecular ion at m/e = 537.

Anal. calc'd for $C_{31}H_{31}N_5O_4$:

C, 69.25 ; H, 5.81 ; N, 13.03 ;

Found : C, 69.48 ; H, 6.18 ; N, 12.96.

65 EXAMPLE 5(R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea

Equimolar amounts of 3(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one and 3-methylphenylisocyanate were mixed in 8 ml of dry tetrahydrofuran at room temperature. The reaction mixture was allowed to stand for 8 hours and was then filtered. The collected solids were washed with tetrahydrofuran and dried in vacuo over P_2O_5 to give analytical product: m.p. 208-210°C.

5 NMR : Confirms structure assignment of product.

HPLC : Greater than 99% pure.

MS : Molecular ion at m/e=399 (M + H) (FAB).

Anal. Calc'd for $C_{24}H_{22}N_4O_2$:

C, 72.34 ; H, 5.56 ; N, 14.06.

10 Found : C, 72.12 ; H, 5.84 ; N, 14.04.

~~X~~ EXAMPLE 6

3(S)-3-(2-(N-carboxymethylindole)carbonylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

15 e

Sodium hydride (0.034 g, 0.71 mmole of a 50% dispersion in mineral oil) and 3(S)-(2-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (0.28 g, 0.69 mmole) were combined in dry, degassed DMF (5 ml) and stirred in an ice bath for 40 minutes. Ethyl bromoacetate (0.077 ml, 0.115 g, 20 0.69 mmole) was added in one portion, and the mixture stirred one hour at room temperature. The DMF was removed in vacuo, and the residue treated with cold, aqueous sodium bicarbonate solution and extracted with ethyl acetate. The ethyl acetate fractions were combined, washed with water, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 7% ether in CH_2Cl_2 . The product fractions were combined and evaporated to dryness in vacuo. The residue (0.25 g, 0.53 mmole) was stirred in CH_3OH (5 ml) and treated with aqueous sodium hydroxide (0.7 ml of a 1 N solution ; 0.7 mmole). The mixture was stirred overnight at room temperature, then acidified with 1 N HCl and extracted with ethyl acetate. The ethyl acetate fractions were combined, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was crystallized from a mixture of acetone, ether, and petroleum ether to give the title compound : (m.p. 165-195°C (indistinct)).

30 TLC : Silica gel (90 : 10 : 1 : 1, CH_2Cl_2 : CH_3OH : HOAc : H_2O), R_f =0.52

NMR : Consistent with structure

HPLC : Greater than 97% pure

M.S. : Molecular ion at M+H=467 (FAB).

Anal. calc'd for $C_{27}H_{22}N_4O_4$: 0.15 $C_4H_{10}O$ -0.45 H_2O

35 C, 68.24 ; H, 5.06 ; N, 11.54 ;

Found : C, 68.21 ; H, 4.85 ; N, 11.47.

~~X~~ EXAMPLE 7

(S)-4-[2-(((2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)amino)carbonyl)-1H-indolyl-1]-butanoic acid

Sodium hydride (0.1 g, 2.5 mmole of a 60% dispersion in mineral oil) and 3(S)-(2-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (1.0 g, 2.45 mmole) were combined in dry, degassed DMF (10 ml) and stirred in an ice bath for 40 minutes. Ethyl-4-bromobutyrate (0.52 g, 2.7 mmole) was added in one portion, and the mixture stirred three hours at room temperature. The DMF was removed in vacuo, and the residue was treated with CH_3OH (350 ml) and aqueous 1 N NaOH (10 ml) and stirred at room temperature for three days. The mixture was evaporated to dryness in vacuo, and the residue was treated with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The aqueous fraction was made acidic with 1N HCl and extracted with ethyl acetate. The ethyl acetate layer was dried over sodium sulfate and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (7% Et_2O/CH_2Cl_2 followed by 540 : 10 : 1 : 1, CH_2Cl_2 : CH_3OH : HOAc : H_2O), R_f =0.23

55 TLC : Silica gel (90 : 10 : 1 : 1, CH_2Cl_2 : CH_3OH : HOAc : H_2O), R_f =0.23

NMR : Consistent with structure

HPLC : Greater than 97% pure

M.S. : Molecular ion at M+H=495 (FAB)

Anal. calc'd for $C_{29}H_{26}N_4O_4$
 C, 70.43 ; H, 5.30 ; N, 11.33 ;
 Found : C, 70.14 ; H, 5.42 ; N, 11.36.

5 ~~X~~ EXAMPLE 8

(RS)-1,3-Dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (15.1 g, 57 mmole) was dissolved in THF (150 ml), cooled in an ice bath, and treated with triethylamine (7.93 ml). A solution of p-nitrophenylchloroformate (11.45g, 57 mmole) in THF (70 ml) was added dropwise. An additional 1 ml of triethylamine and a solution of 2.0g of p-nitrophenylchloroformate in THF were added. After stirring one hour, the mixture was filtered and evaporated to dryness in vacuo. Ether was added and the mixture stirred one hour at room temperature and filtered. The solid was washed twice with ether and dried to give the title compound.

15

EXAMPLE 9

(RS)-3-(((2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)amino)carbonyl)amino)benzoic acid, also known as
(RS)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxyphenyl)-urea.

(RS)-1,3-Dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (5.03 g, 11.2 mmole) and m-aminobenzoic acid (2.4 g, 17.5 mmole) were combined in DMF (120 ml), treated with triethylamine (4.2 ml), and stirred in an oil bath thermostatted at 45° for 18 hours. The DMF was removed in vacuo and the residue was dissolved in boiling methanol. The crystallized product was recrystallized from hot methanol : (m.p. 175-180°C).

25

TLC : Silica gel (90 : 10 : 1 : 1, CH_2Cl_2 : CH_3OH : HOAc : H_2O), R_f =0.5

NMR : Consistent with title structure

HPLC : Greater than 97.8% pure

30

M.S. : M+H at m/e=429 (FAB)

Anal. calc'd for $C_{24}H_{20}N_4O_4 \cdot 1.15H_2O$

C, 64.17 ; H, 5.00 ; N, 12.47 ;

Found : C, 64.20 ; H, 5.20 ; N, 12.60.

35

EXAMPLE 10

(R)-3-(((2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)amino)carbonyl)amino)benzoic acid

40 Benzyl alcohol (10 g, 92.6 mmole) was treated with a solution of m-nitrobenzoyl chloride (17.5 g, 94.5 mmole) in ether (50 ml) added dropwise. The mixture was stirred at room temperature for eighteen hours, then washed twice with aqueous sodium bicarbonate, dried over sodium sulfate, and filtered. The filtrate was evaporated to dryness in vacuo and the residue chromatographed on silica gel eluted with 1 : 1 CH_2Cl_2 : hexane. The product fractions were combined and evaporated to dryness in vacuo. A portion (5.2 g, 20.2 mmole) of the resulting benzyl m-nitrobenzoate was dissolved in ethanol and hydrogenated over platinum oxide (70 mg) at 50 psi of H_2 . The resulting mixture was filtered and evaporated to dryness in vacuo to give benzyl m-aminobenzoate.

45

(R)-1,3-Dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one was prepared using the procedure of Example 8 wherein 3-(R)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one was employed in place of the (RS) compound.

50

55 To benzyl m-aminobenzoate (0.25 g, 1.10 mmole) in DMF (17 ml) was added triethylamine (0.23 ml) followed by a solution of (R)-1,3-dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one(0.469 g, 1.09 mmole) in DMF (23 ml) containing triethylamine (0.23 ml). The mixture was stirred at room temperature for one hour, then treated with water, made acidic with 1N HCl, and extracted with ethyl acetate. The ethyl acetate layers were combined, washed with aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 500 ml each of 5%, 6%, 7%, 9%, 10%, and 12% ether in CH_2Cl_2 . The product fractions were combined and evaporated to dryness in vacuo. A portion of the residue (81.2 mg, 0.086 mmole) was dissolved in

ethanol (70 ml) and hydrogenated over palladium/charcoal (20 mg) at 50 psi of H₂. The mixture was filtered and evaporated to dryness in vacuo to provide the title compound.
 TLC : Silica gel (90 : 10 : 1 : 1, CH₂Cl₂ : CH₃OH : HOAc : H₂O) identical to material prepared as in Example 9.

5 EXAMPLE 11(S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphonyl)-urea

The procedure of Example 5 was carried out using 3(S)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one in place of the 3(R) enantiomer to give the title compound : m.p. 158-160°C.
 TLC : Silica gel (95 : 5 : 0.5, CHCl₃ : CH₃OH : conc. NH₃), R_f=0.52
 NMR : Consistent with title structure.
 HPLC : Greater than 98.5% pure
 MS : Molecular ion at m/e=398
 15 Anal. Calc'd for C₂₄H₂₂N₄O₂ :
 C, 72.34 ; H, 5.56 ; N, 14.06 ;
 Found : C, 72.34 ; H, 5.75 ; N, 14.02.

EXAMPLE 121,3-Dihydro-5-(2-pyridyl)-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one

2-Benzylmethylpyridine was prepared from 2-picoline and phenyllithium according to the procedure of Goldberg et al.¹ This compound was converted to the phenylhydrazone and thence to 2-phenyl-3-2'-pyridylindole as described by Ockenden et al.² 2-Phenyl-3-2'-pyridylindole was converted to 2-o-benzamidobenzoylpyridine using the chromic anhydride oxidation procedure described by Schofield et al.³ 2-o-Benzamidobenzoylpyridine was deacylated to provide 2-o-aminobenzoylpyridine using the procedure of Ockenden et al.²
 2-o-aminobenzoylpyridine was converted to 1,3-dihydro-5-(2-pyridyl)-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one using the procedure described by Bock et al.⁴ for preparation of 1,3-dihydro-5-phenyl-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one from 2-aminobenzophenone.
 1Goldberg, N.N. et al., J. Am. Chem. Soc., 73, 4301 (1951).
 2Ockenden, D.W. et al., J. Chem. Soc., 1953, 3440.
 3Schofield, K. et al., J. Chem. Soc., 1949, 796.
 4Bock, M.G. et al., J. Org. Chem., 52, 3232 (1987).

EXAMPLE 131,3-Dihydro-5-(2-fluorophenyl)-3(R)-[3'-(1'-methyl-indolyl)-methyl]-1-methyl-2H-1,4-benzodiazepin-2-one (A)
and 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl) methyl-1-methyl-2H-1,4-benzodiazepin-2-one (B)

A. 1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one (0.85 g, 2.2 mmole) and sodium hydride (0.11 g of a 50% suspension in mineral oil, 2.3 mmole) were stirred in 10 ml of dry, degassed dimethylformamide under nitrogen in an ice bath : After 40 minutes, methyl iodide (0.14 mL = 2.25 mmole) was added in one portion. The mixture was stirred for 1.5 hours at room temperature, then poured into 100 ml of water and extracted with methylene chloride (CH₂Cl₂) (3 x 30 mL). The CH₂Cl₂ layers were washed with water, dried over potassium carbonate, filtered and evaporated in vacuo. The residue was chromatographed on 9" (23 cm) of silica gel (250-400 mesh) in a 55 mm diameter column eluted with 4% (v/v) diethyl ether in CH₂Cl₂. The first product eluted was A which was obtained as a glass upon evaporation. The solid was dried in vacuo at room temperature : (m.p. 97-100°C(↑)).

The compound showed a single component by thin layer chromatography (R_f=0.57, silica gel plate eluted with 10% (v/v) diethyl ether in CH₂Cl₂) and by HPLC (98%). The NMR spectrum was consistent with the title structure and verified the presence of CH₂Cl₂. The mass spectrum showed a molecular ion at m/e=411.
 Anal. Calc'd. for C₂₈H₂₂FN₃O-0.1 CH₂Cl₂

55 C, 74.64 ; H, 5.33, N, 10.01.
 Found : C, 74.69 ; H, 5.32 ; N, 9.63.

B. The second component eluted was the monomethyl compound B which was obtained as a foam (0 : 66 g) upon evaporation. Crystallization from hexane/CH₂Cl₂ gave analytical material : (m.p. 80-85°C(↑)).

The compound showed a single component by thin layer chromatography (silica gel plates eluted with 4% (v/v) diethyl ether in CH_2Cl_2) and by HPLC (99%). The NMR spectrum was consistent with the title structure and verified the presence of CH_2Cl_2 .

Anal. Calc'd for $\text{C}_{25}\text{H}_{20}\text{FN}_3\text{O} \cdot 0.75 \text{CH}_2\text{Cl}_2$:

5 C, 67.06; H, 4.70; N, 9.11;

Found: C, 67.04; H, 4.81; N, 9.14.

EXAMPLE 14

3-(RS)-Amino-1,3-dihydro-1-methyl-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-5-(2-pyridyl)-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one was methylated using the procedure of example 13 wherein 1,3-dihydro-5-(2-pyridyl)-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one was substituted for no-2H-1,4-benzodiazepin-2-one. The crude product was 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)-methyl-2H-1,4-benzodiazepin-2-one. The crude product was chromatographed on silica gel eluted with 1.2 L each of 90 : 10 : 0, 85 : 14 : 1, and 83.5 : 15 : 1.5 of CH_2Cl_2 : acetone : methanol. The product fractions were combined and evaporated to dryness in vacuo. The residue was added to a stirred suspension of 10% Palladium/charcoal in 95% methanolic formic acid and stirred at room temperature for one hour. The mixture was filtered and the solvent removed in vacuo. The residue was treated with aqueous sodium carbonate and extracted with ethyl acetate. The aqueous fraction was evaporated to dryness in vacuo, and extracted three times with ethyl acetate. The ethyl acetate layers were combined, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo to give the title compound.

EXAMPLE 15

3-(RS)-Amino-1,3-dihydro-1-methyl-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-5-(4-pyridyl)-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one was prepared using the procedure of Example 12 wherein 4-picoline was substituted for 2-picoline. Methylation and hydrogenolysis according to the method of Example 14 provided the title compound.

EXAMPLE 16

3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3(S)-(-)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (595 mg, 2.24 mmole) was dissolved in CH_2Cl_2 (15 ml) and treated with 2-indolecarbonyl chloride (403 mg, 2.24 mmole) followed by triethylamine (227 mg, 2.24 mmole). The mixture was stirred at room temperature for 30 minutes and concentrated in vacuo. The residue was chromatographed on silica gel (5% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) and the combined product fractions evaporated to dryness in vacuo. Three times, Et_2O (15 ml) was added and evaporated in vacuo to give the title compound: (m.p. 168-185°C).

TLC: Silica gel (6%, $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$), R_f =0.23

NMR: Consistent with structure

HPLC: Greater than 99% pure

45 M.S.: Molecular ion at m/e = 408
 $[\alpha]_D^{25} = -103^\circ$ (0.0078 g/ml, CH_2Cl_2)

Anal. calc'd for $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_2$

C, 73.51; H, 4.94; N, 13.72;
 Found: C, 73.38; H, 4.80; N, 13.66.

50

EXAMPLE 17

1,3-Dihydro-3(RS)-(2-indolecarbonylamino)-1-methyl-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one

55 The title compound was prepared using the procedure of example 16 wherein 3-(RS)-amino-1,3-dihydro-1-methyl-5-(4-pyridyl)-2H-1,4-benzodiazepin-2-one was substituted for 3(S)-(-)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. The crude product was purified by chromatography on silica gel, eluted with 5% methanol in CH_2Cl_2 . The product fractions were evaporated to dryness in vacuo to give the title com-

pound : (m.p. 275-283°C).

TLC : Silica gel (5% CH₃OH in CH₂Cl₂) R_f=0.28

NMR : Consistent with structure

HPLC : Greater than 96.2% pure

5 M.S. : Molecular ion at m/e = 409

Anal. calc'd for C₂₄H₁₉N₅O₂·0.3CH₃OH·0.2H₂O

C, 69.05 ; H, 4.91 ; N, 16.57 ;

Found : C, 69.02 ; H, 4.71 ; N, 16.54.

10 EXAMPLE 18

X 1,3-Dihydro-1-(2-methylpropyl)-5-(2-pyridyl)-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one

15 1,3-Dihydro-5-(2-pyridyl)-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one was converted to the 1-(2-methylpropyl) derivative using the procedure of example 13 wherein 1,3-dihydro-5-(2-pyridyl)-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one was substituted for 1,3-dihydro-5-(2-fluorophenyl)-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one, and 1-bromo-2-methylpropane was substituted for methyl iodide. The crude product was purified by chromatography on silica gel eluted with 1% methanol in CH₂Cl₂. The combined product fractions were evaporated to dryness in vacuo.

20

EXAMPLE 19

3-(RS)-Amino-1,3-dihydro-1-(2-hydroxyethyl)-5-phenyl-2H-1,4-benzodiazepin-2-one

25

1,3-Dihydro-5-phenyl-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one¹ (0.25 g, 0.65 mmole) was dissolved in DMF (5 ml) stirred in an ice bath. The solution was treated with sodium hydride (32.7 mg, 0.681 mmole of a 50% dispersion in mineral oil) and the mixture stirred for forty minutes in the cold. Oxirane gas was bubbled into the mixture for five minutes, and the resulting mixture heated on a steam bath for one hour. The DMF was removed in vacuo. The residue was treated with water and extracted with ethyl acetate. The ethyl acetate layers were combined, washed with water, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 35% ethyl acetate in methylene chloride. The combined product fractions were evaporated to dryness in vacuo. The residue was dissolved in CH₂Cl₂, cooled in an ice bath, and saturated with HBr gas. The mixture was evaporated to dryness in vacuo, treated with a minimum volume of water and extracted repeatedly with ethyl acetate. The ethyl acetate layers were combined, dried over sodium sulfate, filtered, and evaporated to dryness in vacuo to give the title compound.

30

¹Bock, M.G., et al., J. Org. Chem., 52, 3232 (1987).

35

EXAMPLE 20

(RS)-N-(2,3-Dihydro-1-(2-hydroxyethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide

40

3-(RS)-Amino-1,3-dihydro-1-(2-hydroxyethyl)-5-phenyl-2H-1,4-benzodiazepin-2-one (69.0 mg, 0.234 mmole), indole-2-carboxyl chloride (43.1 mg, 0.240 mmole) and triethylamine (33.3 μ l, 0.240 mmole) were combined in CH₂Cl₂ (3 ml). The reaction was stirred for 10 minutes at room temperature then chromatographed on silica gel (14% acetone in CH₂Cl₂). The product fractions were combined and evaporated to dryness in vacuo. The residue was triturated with Et₂O to yield the title compound : (m.p. 160-171°C).

45

TLC : silica gel (15% acetone in CH₂Cl₂) R_f=0.27

NMR : Consistent with structure

HPLC : 97.6%

M.S. : Molecular ion at m/e=438

Anal. Calc'd for C₂₉H₂₂N₄O₃·0.1C₄H₁₀O·0.25H₂O

50 C, 70.40 ; H, 5.26 ; N, 12.44

55 Found : C, 70.40 ; H, 5.16 ; N, 12.15

EXAMPLE 21

(RS)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-9H-pyrido(3,4-b)indol-3-yl-urea

5 A solution of (RS)-1,3-dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (100 mg, 0.232 mmole) and 3-Amino- β -carboline¹ (45.8 mg, 0.250 mmole) in DMF (5 ml) was treated with triethylamine (48.4 μ l, 0.348 mmole) and warmed to 45°C for 16 hours. After removal of DMF in vacuo, the residue was dissolved in CH₂Cl₂ and chromatographed on silica gel (25% acetone in CH₂Cl₂). The product fractions were combined and stripped and the title compound crystallized from EtOAc : (m.p. 281-283°C).

10 TLC : silica gel (160/10/1 of CH₂Cl₂/MeOH/conc. NH₄OH) R_f = 0.24

10 NMR : Consistent with structure

10 HPLC : 99.3% pure

10 M.S. : M+H⁺ = 475 (FAB)

10 Anal. Calc'd for C₂₈H₂₂N₆O₂·0.20C₄H₈O₂ : C, 70.28 ; H, 4.83 ; N, 17.08

15 Found : C, 70.10 ; H, 4.55 ; N, 17.24

15 ¹ Dodd, R. H., et al. J. Med. Chem. 28 824 (1985)

EXAMPLE 22(R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-9H-pyrido(3,4-b)indol-3-yl-urea

20 (R)-1,3-Dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one was prepared according to the procedure of Example 8 wherein 3-(R)-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one was substituted for the 3-(RS) compound. A solution of (R)-1,3-dihydro-1-methyl-3-(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (165 mg, 0.382 mmole) in DMF (4 ml) was treated with a DMF (3 ml) solution of 3-amino- β -carboline¹ (70 mg, 0.382 mmole) and triethylamine (79.7 μ l, 0.573 mmole). The reaction was warmed to 45°C for 1.5 hours after which a second portion of 3-amino- β -carboline (70 mg, 0.382 mmole) in DMF (3 ml) was added. The reaction was again heated to 45°C for 1.5 hours and then stirred at 25° for 16 hours.

30 After removal of DMF in vacuo, the residue was treated with H₂O and extracted with EtOAc (3x). The organic layers were combined, washed with brine (1x), dried over Na₂SO₄, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (30% acetone in CH₂Cl₂). The product fractions were combined and evaporated to dryness in vacuo. The residue was dissolved in EtOAc, dried over Na₂SO₄, filtered and allowed to stand. A small portion of the racemate of the title compound was collected by filtration.

35 The filtrate was evaporated to dryness in vacuo and the residue was chromatographed on silica gel (180/10/1/1 of CH₂Cl₂/MeOH/H₂O/HOAc). The product fractions were combined, washed with aqueous sodium carbonate, brine (1x), dried over Na₂SO₄, filtered and evaporated to dryness in vacuo. The residue was evaporated from EtOAc (1x) and Et₂O (2x), then triturated with Et₂O to give the title compound : (m.p. 214-228°C).

35 TLC : silica gel (180/10/1/1 of CH₂Cl₂/MeOH/H₂O/HOAc) R_f = 0.25

40 NMR : Consistent with structure

40 HPLC : 98.8%

40 Optical purity : greater than 99.4% (chiral column HPLC)

40 Anal. Calc'd for C₂₉H₂₂N₆O₂·0.45H₂O : C, 69.68 ; H, 4.78 ; N, 17.41

45 Found : C, 69.68 ; H, 4.44 ; N, 17.43

45 ¹ Dodd, R. M. et al. J. Med. Chem. 28 824 (1985)

EXAMPLE 23(RS)-N-(6-Amino-3-pyridyl)-N'-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-urea

2,5-Diaminopyridine dihydrochloride (45.5 mg, 0.250 mmole), (RS)-1,3-dihydro-1-methyl-3-(*p*-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (100 mg, 0.232 mmole) and triethylamine (110 μ l, 0.79 mmole) were combined in DMF (8 ml) and stirred at room temperature for 16 hours. After removal of DMF in vacuo, the residue was treated with 1N NaOH (aqueous) and extracted with EtOAc (3x). The organic layers were combined, washed with brine (1x), dried over Na_2SO_4 , filtered and evaporated to dryness in vacuo. The crude residue was chromatographed on silica gel eluted with 7% MeOH in CH_2Cl_2 . The product fractions were combined and evaporated to dryness in vacuo. The residue was crystallized from EtOAc diluted with Et_2O to give the title compound : (m.p. 165-175°C).
 5 TLC : silica GF (90/10/1/1 of CH_2Cl_2 /MeOH/ H_2O /HOAc) R_f 0.22

10 N MR : consistent with structure
 HPLC : 96.3%
 M.S. : $M+H=$ 401 (FAB)
 Anal. Calc'd for $\text{C}_{22}\text{H}_{20}\text{N}_8\text{O}_2\cdot 0.35\text{H}_2\text{O}$
 C, 64.96 ; H, 5.13 ; N, 20.66
 15 Found : C, 65.05 ; H, 5.20 ; N, 20.66.

EXAMPLE 24

(RS)-N-(2,3-Dihydro-1-methyl-2-oxo-5-(2-pyridyl)-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide

20 A solution of 3-(RS)-amino-1,3-dihydro-1-methyl-5-(2-pyridyl)-2H-1,4-benzodiazepin-2-one (20 mg, 0.075 mmole) in CH_2Cl_2 (2 ml) was treated with indole-2-carbonyl chloride (14.4 mg, 0.080 mmole) and the pH adjusted to 9.5 with triethylamine (11.5 μ l, 0.085 mmole). The reaction was stirred 10 minutes and chromatographed on silica gel (25/10/1/1 of CH_2Cl_2 /MeOH/ H_2O /HOAc). The combined product fractions were stripped to dryness, 25 dissolved in EtOAc, washed with water (1x), and brine, dried over Na_2SO_4 , filtered and stripped to dryness. The title compound was crystallized from Et_2O : (m.p. 274-277°C)
 TLC : silica gel (25/10/1/1 or CH_2Cl_2 /MeOH/ H_2O /HOAc) R_f 0.29
 NMR : consistent with structure
 HPLC : 98.8%
 30 M.S. : $M+H=$ 410 (FAB)
 Anal. Calc'd for $\text{C}_{24}\text{H}_{19}\text{N}_5\text{O}_2\cdot 0.1\text{C}_4\text{H}_{10}\text{O}\cdot 1.4\text{H}_2\text{O}$
 C, 66.29 ; H, 5.20 ; N, 15.84
 Found : C, 66.12 ; H, 4.72 ; N, 15.55.

35 EXAMPLE 25

(RS)-N-(2,3-Dihydro-1-(2-methylpropyl)-2-oxo-5-(2-pyridyl)-1H-1,4-benzodiazepin-3-yl)-N'-(3-methyl-phenyl)-urea

40 1,3-Dihydro-1-(2-methylpropyl)-5-(2-pyridyl)-3(R,S)-[(benzyloxycarbonyl)-amino]-2H-1,4-benzodiazepin-2-one (80 mg, 0.181 mmole) was dissolved in CH_2Cl_2 (7 ml) with HOAc (0.5 ml), cooled to 0°C, and HBr (gas) bubbled into the solution for 30 minutes. The reaction was flushed with N_2 (gas) for 10 minutes, stripped in vacuo, and the residue treated with 1N NaOH (aqueous) and extracted with EtOAc (4x). The organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated to 20 ml and the EtOAc solution treated with m-tolylisocyanate (25.8 μ l, 0.200 mmole). After stirring at 25°C for 15 minutes the reaction mixture was concentrated to 4 ml and the title compound obtained via crystallization : (m.p. 236-239°C).
 TLC : silica gel (80/10/1 of CH_2Cl_2 /MeOH/Conc. NH_4OH) R_f 0.72
 NMR : consistent with structure
 HPLC : 99.0%
 50 M.S. : $M+H=$ 442 (FAB)
 Anal. Calc'd for $\text{C}_{28}\text{H}_{27}\text{N}_5\text{O}_2\cdot 0.25\text{H}_2\text{O}$
 C, 70.01 ; H, 6.21 ; N, 15.70
 Found : C, 70.05 ; H, 6.07 ; N, 15.70.

55 EXAMPLE 26

(RS)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(5-indanyl)urea.

(RS)-1,3-dihydro-1-methyl-3(p-nitrophenyloxycarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (100 mg, 0.232 mmols) and 5-aminoundane (33.3 mg, 0.250 mmols) were combined in DMF (3 ml), treated with triethylamine (48.7 μ l), and stirred in an oil bath thermostated at 50°C for 16 hours. The DMF was removed in vacuo and the residue treated with H₂O and extracted with ethyl acetate (3x). The organic extracts were combined, washed with brine (1X), dried over Na₂SO₄, filtered, and stripped to dryness. Crystallization from ethyl acetate gave the title compound : (mp. 233-5°C).

5 TLC : Silica GF (160/10/1 of CH₂Cl₂/MeOH/Conc. NF₄OH) R_f=0.52

NMR .Consistent with title structure

HPLC : 99.7% pure

10 M.S. : M+H at m/e= 425 (FAB)

Anal. Calc'd for C₂₈H₂₄N₄O₂ :

C, 73.56 ; H, 5.70 ; N, 13.20.

Found : C, 73.24 ; H, 5.42 ; N, 13.56.

15 EXAMPLE 27

1,3-Dihydro-3-(5-hydroxyindole-2-carbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

20 3(S)-(-)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (0.14 g, 0.53 mmol) and 5-hydroxyindole-2-carboxylic acid (0.11 g, 0.63 mmol) were combined in a mixture of CH₂Cl₂ (5 ml) and DMF (1 ml). EDC (0.1 g, 0.56 mmol) was added followed by Et₃N sufficient to render the mixture basic (pH 8) to moistened pH detector sticks (E. Merck). The mixture was stirred at ambient temperature for 6 hours, then evaporated to dryness in vacuo. The residue was diluted with aqueous citric acid and extracted with EtOAc. The EtOAc layer was washed twice with saturated sodium bicarbonate which had been diluted 1 : 1 with water, then dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was dried in vacuo at 90°C overnight to give the title compound : (mp 120-130°C (↑)).

TLC : Silica gel (10% CH₃OH in CH₂Cl₂) R_f = 0.73

NMR : Consistent with structure, H₂O observed.

HPLC : Greater than 94.5% pure

30 M.S. Molecular ion at m/e = 424

Anal. Calc'd for C₂₅H₂₀N₄O₃·0.55H₂O :

C, 69.12 ; H, 4.90 ; N, 12.90 ;

Found : C, 69.34 ; H, 5.01 ; N, 12.52.

35 EXAMPLE 28

1,3-Dihydro-3-(5-carboxymethoxyindole-2-carbonyl-amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

40 1,3-Dihydro-3-(5-hydroxyindole-2-carbonyl-amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (0.1 g, 0.236 mmol) and iodoacetic acid (0.044 g, 0.236 mmol) were combined in dry DMF (2 ml) and treated with sodium hydride (18.8 mg of a 60% suspension in mineral oil ; 0.472 mmol). The mixture was stirred at ambient temperature for 1 hour, then evaporated to dryness in vacuo. To the residue were added water, dilute sodium bisulfite solution, then saturated sodium bicarbonate. The aqueous phase was washed with EtOAc, made acidic with 6N HCl, and extracted with EtOAc. The acid layer extract was dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 180 : 10 : 1 : 1 of CH₂Cl₂ : MeOH : HOAc : H₂O. The product fractions were evaporated to dryness in vacuo and the residue triturated with ether to give the title compound which was dried in vacuo at 90°C overnight : (mp 150-180°C (↑)).

TLC : Silica gel (180 : 10 : 1 : 1 of CH₂Cl₂ : CH₃OH : HOAc : H₂O) R_f = 0.19

NMR : Consistent with structure, Et₂O and H₂O observed.

50 HPLC : Greater than 83.2% pure

M.S. M + H at m/e = 483 (FAB)

Anal. Calc'd for C₂₇H₂₂N₄O₅·0.05Et₂O·0.7H₂O :

C, 65.49 ; H, 4.83 ; N, 11.23 ;

Found : C, 65.53 ; H, 4.49 ; N, 11.10.

55 EXAMPLE 29

N-(2,3-Dihydro-1-(2-hydroxyethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea

5 3-(RS)-Amino-1,3-dihydro-1-(2-hydroxyethyl)-5-phenyl-2H-1,4-benzodiazepin-2-one (0.45 g, 1.5 mmol) was dissolved in THF (10 ml) and treated with 3-methylphenylisocyanate (0.207 g, 1.55 mmol), and the mixture stirred at ambient temperature for 1 hour, then evaporated to dryness in vacuo. The residue was chromatographed on silica gel eluted with 20% acetone in CH_2Cl_2 . The product fractions were evaporated to dryness in vacuo and the residue triturated with ether to give the title compound which was dried in vacuo at 65°C for 2 hours : (mp 138-154°C).

TLC : Silica gel (90 : 4 : 0.4 of CH_2Cl_2 : CH_3OH : HOAc : H_2O) R_f = 0.24

NMR : Consistent with structure.

HPLC : Greater than 99.7% pure

10 M.S. M + H at m/e = 429 (FAB)

Anal. Calc'd for $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_3$: 0.07 Et_2O -0.4 H_2O :

C, 68.87 ; H, 5.83 ; N, 12.71 ;

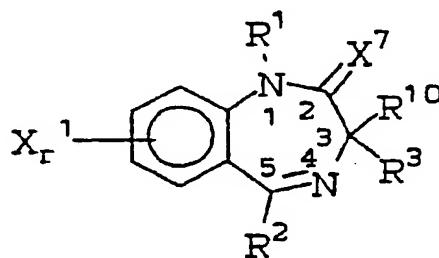
Found : C, 68.83 ; H, 5.63 ; N, 12.58.

15 While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations or modifications, as come within the scope of the following claims and its equivalents.

20 Claims

1. A pharmaceutical composition useful in treatment of panic disorder or other neurological disorders involving anxiety, comprising an effective amount of a CCK and/or gastrin antagonist compound of the formula :

25

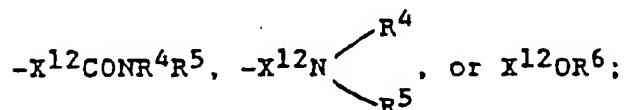


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35 wherein :

R^1 is H, C_{1-6} linear or branched alkyl, $\text{X}^{12}\text{-cycloalkyl}$, $-\text{X}^{12}\text{COOR}^6$,

40



45

R^2 is substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, carboxyl, nitro or $-\text{CF}_3$) ; $-\text{X}^{12}\text{COOR}^6$; 2-, 3-, 4-pyridyl ;

50



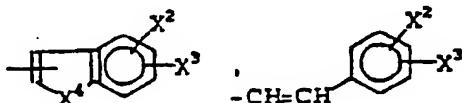
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R^4 and R^5 are independently R^6 or in combination with the N of the NR^4R^5 group form an unsubstituted or mono- or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH₃, and the substituent(s) is/are independently selected from C_{1-4} alkyl ;

R^6 is H, C_{1-6} straight or branched-chain alkyl or cycloalkyl ;

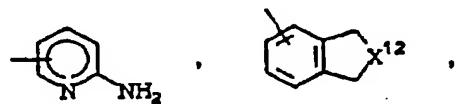
R⁷ is α - or β -naphthyl, substituted or unsubstituted phenyl (wherein the substitutents may be 1 to 2 of halo, -NO₂, -OH, -NR⁴R⁵, loweralkyl, CF₃, CN, COOR⁶, X¹²COOR⁸, X¹²OR⁸, or loweralkoxy), 2-, 3-, 4-pyridyl,

5

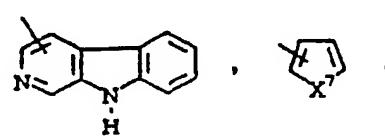


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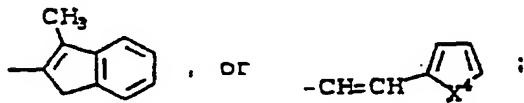
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30

R⁸ is H, loweralkyl, cycloloweralkyl, X¹²COOR⁸;

35

R¹⁰ is H or -OH where R³ is CR⁷, otherwise it is H;
r is 1 or 2;

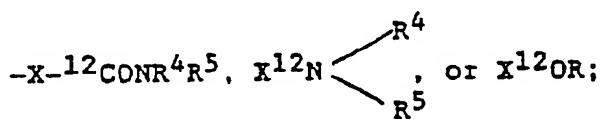
40

X¹ is H, -NO₂, CF₃, loweralkyl or halo;
X² and X³ are independently H, -NO₂, OH, halo, loweralkyl, or loweralkoxy, X¹²COOR⁸, COOR⁸, or OX¹²COOR⁸;
X⁴ is O, or NR⁸;
X⁷ is O;
X¹² is C₁₋₅ linear or branched chain alkyl, or the pharmaceutically acceptable salt thereof.

45

2. The pharmaceutical composition of Claim 1 wherein:
R¹ is H, C₁-C₄ linear or branched chain alkyl, X¹²-cycloalkyl, -X¹²COOR⁸,

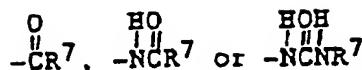
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55

R² is substituted or unsubstituted phenyl (wherein the substituent may be 1 or 2 of halo, loweralkyl, nitro, -CF₃), 2-, 3-, 4-pyridyl, or X¹²COOR⁸;

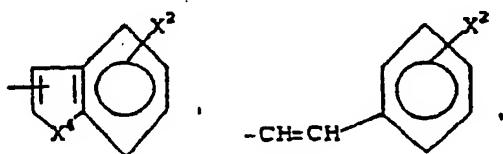
R³ is



5 R⁴ and R⁵ are independently R⁶ or in combination with the N of the NR⁴R⁵ group form an unsubstituted
or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7
membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may
contain a second heteroatom selected from O and NCH₃ and the substituent(s) is/are independently
selected from C₁₋₄ alkyl ;

10 R⁶ is H, C₁-C₃ straight chain alkyl ;
R⁷ is α - or β -naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of
halo, -NO₂, NH₂, methyl, ethyl, CF₃, CN, COOH,
X¹²OR⁶, or lower alkoxy), 2-,3-,4-pyridyl,

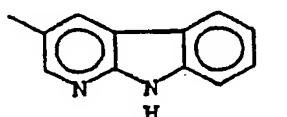
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R¹⁰ is H, or OH when R³ is CR⁷, otherwise R¹⁰ is H;
x is 1 or 2;

40

X¹ is H, -NO₂, CF₃, loweralkyl or halo ;
X² is H, -NO₂, halo, OH, loweralkoxy, loweralkyl,
X¹²COOH, or OCH₂COOH ;
X⁴ is O, NH, NCH₃, NX¹²COOH ;
X⁷ is O ;

45

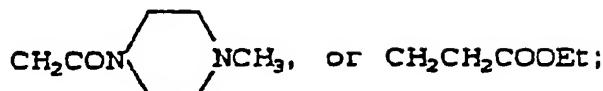
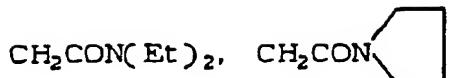
X¹² is C₁₋₆ linear alkyl ;
or pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of Claim 2 wherein :

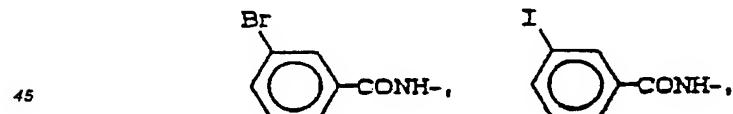
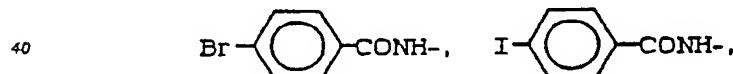
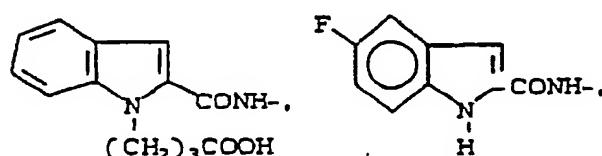
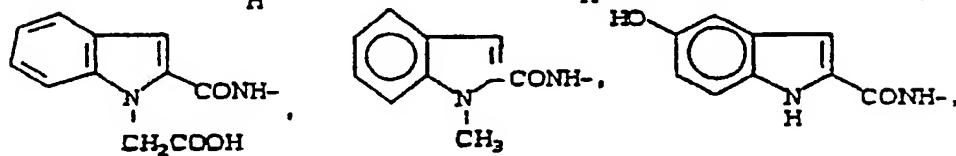
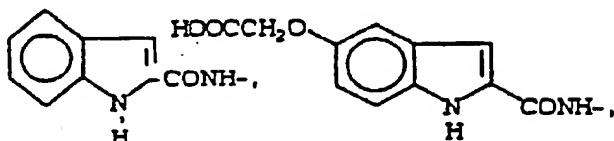
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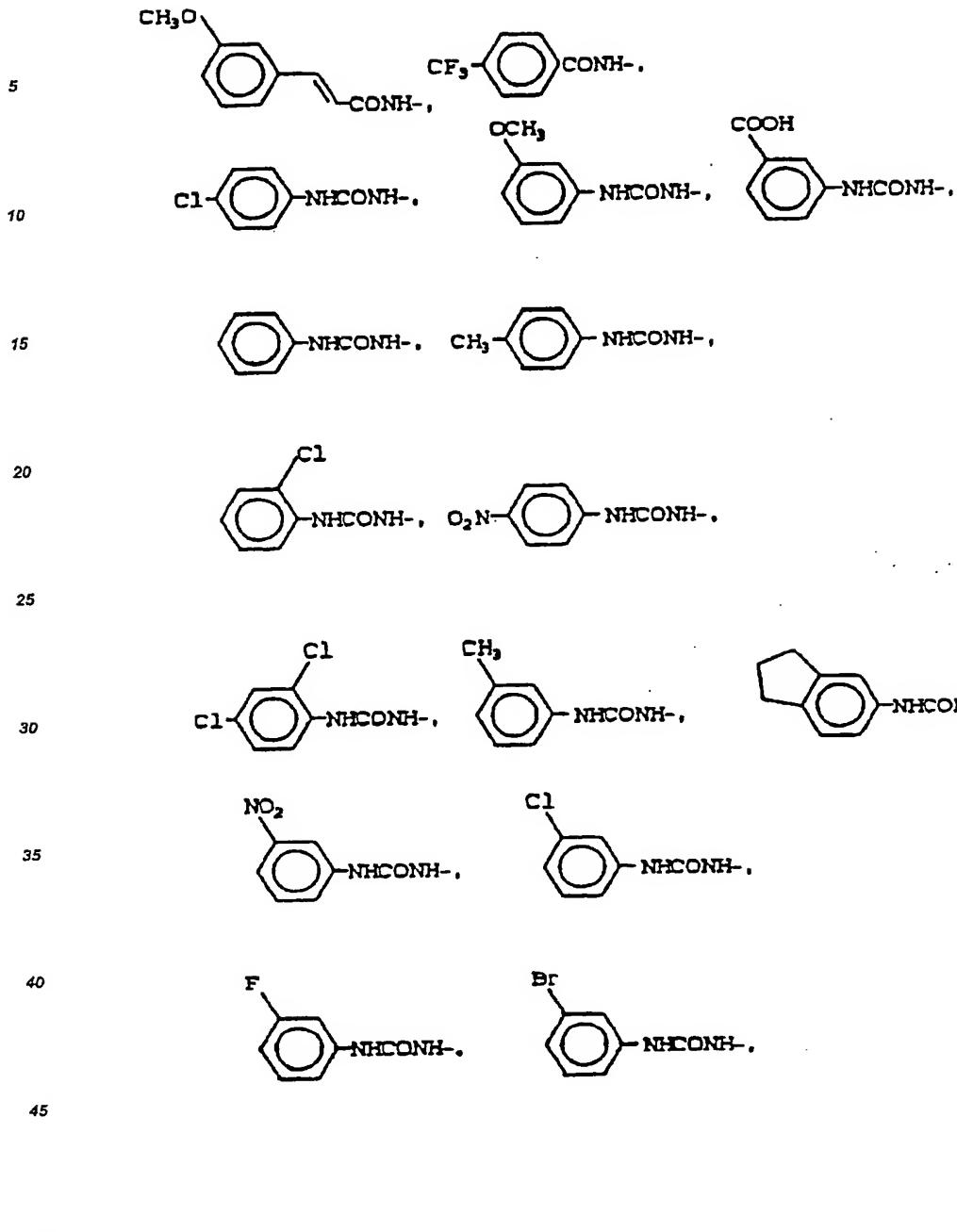
R¹ is H, CH₃, CH₂CH₃, CH₂CH(CH₃)₂, CH₂——, CH₂CH₂OH, CH₂COOH, CH₂COOEt,

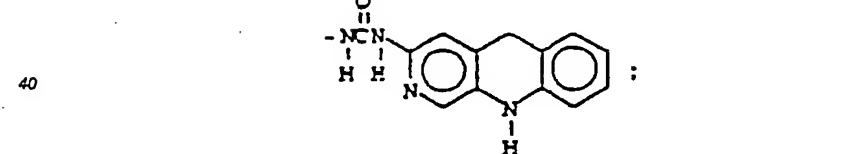
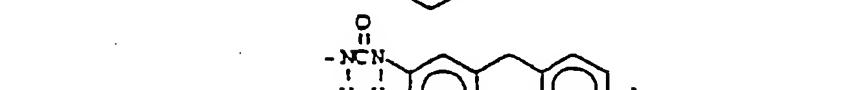
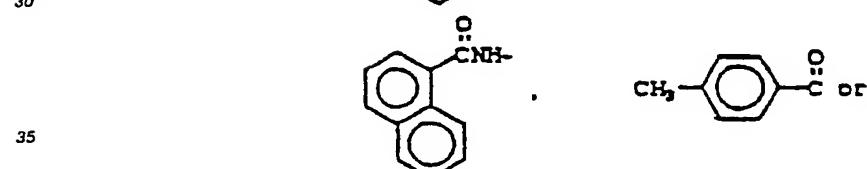
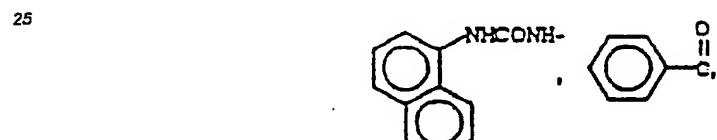
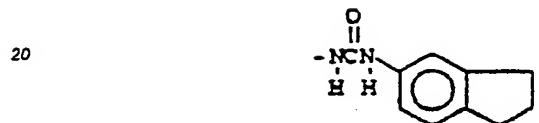
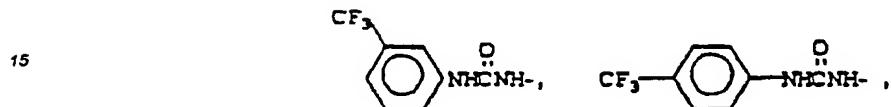
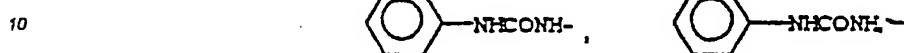
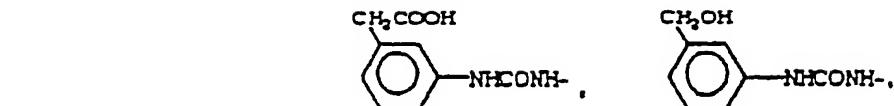
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15 R^2 is phenyl, 2-F-phenyl, 4-CH₃-phenyl, 2-, 3-, or 4-pyridyl ;
 R^3 is







45

50

R^{10} is H or -OH, when R^3 is PhC or $CH_3-C_6H_4-C$ or otherwise $R^{10}=H$;

50: CC(=O)c1ccc(C)cc1

55

X^1 is H, Cl; or - CH_3 ;
 X^7 is O;
 or pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition useful in the treatment of panic disorder or other neurological disorders involving anxiety, comprising an effective amount of the CCK and/or gastrin antagonist compound which

is

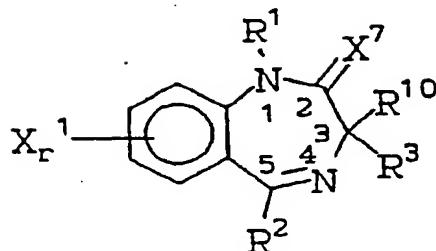
3-N-(2,3-Dihydro-1-methyl-2-oxo-5-(p-tolyl)-1H-1,4-benzodiazepin-3-yl)-1H-Indole-2-carboxamide,
 3-N-(2,3-Dihydro-1,9-dimethyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,
 3-N-(2,3-Dihydro-1,8-dimethyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,
 3-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-3-phenyl-2-propenamide,
 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(2-chlorophenyl)-urea,
 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-
 1,3-Dihydro-3-(5-carboxymethyloxyindole-2-carbonyl-amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-
 2-one,
 1,3-Dihydro-3-(5-hydroxyindole-2-carbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one,
 10 (S)-N-(5-(2-Fluorophenyl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-4-(trifluoromethyl)-be-
 nzamide,
 3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-o-
 ne,
 3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one,
 15 3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one,
 3-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-2-amino-4-chlorobenzamide,
 4-Bromo-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-benzamide,
 20 1,3-Dihydro-5-(2-fluorophenyl)-1-methyl-3(RS)-[2'-(1'-methylindole)carbonylamino]-2H-1,4-benzodiazep-
 in-2-one,
 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methoxyphenyl)-urea,
 1,3-dihydro-1-methyl-3(RS)-[2-(1-methylindole)-carbonylamino]-5-phenyl-2H-1,4-benzodiazepin-2-one,
 Carboxymethyl-1,3-dihydro-3(RS)-(2-indolecarbonyl-amino)-5-phenyl-2H-1,4-benzodiazepin-2-one,
 25 3(S)-(+)-1,3-Dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-on-
 e,
 3-[(((3-Methoxyphenyl)amino)carbonyl)amino]-N,N-diethyl-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodia-
 zepin-1-acetamide,
 1-((3(((4-Chlorophenyl)amino)carbonyl)amino)-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-
 -acetyl)pyrrolidine,
 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea,
 30 3-[((2-Chlorophenyl)amino)carbonyl]amino)-N,N-diethyl-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodia-
 zepin-1-acetamide,
 35 5-[(R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-bromophenyl)-urea, or
 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(4-methylphenyl)-urea,
 (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxyphenyl)-urea,
 (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H,1,4-benzodiazepin-3-yl)-N'-(5-indanyl)-urea,
 N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxymethylphenyl)urea,
 40 (R)-N-(6-Amino-3-pyridinyl)-N'-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)urea, or
 N-(2,3-Dihydro-1-(2-hydroxymethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)ur-
 ea, or pharmaceutically acceptable salt thereof.

45 5. The pharmaceutical composition of Claim 1, wherein the compound is
 3(S)-(-)-1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, or
 (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or
 pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition useful in the treatment of panic disorder or other neurological disorders
 involving anxiety, comprising an effective amount of the CCK and/or gastrin antagonist compound
 3(S)-(-)-1,3-dihydro-3-(2-indolecarbonyl amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, or phar-
 maceutically acceptable salt thereof.

50 7. A pharmaceutical composition useful in the treatment of panic disorder or other neurological disorders
 involving anxiety, comprising an effective amount of the CCK and/or gastrin antagonist compound
 (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or
 pharmaceutically acceptable salt thereof.

55 8. The use of a CCK and/or gastrin antagonist compound of the formula :



wherein :

R¹ is H, C₁₋₆ linear or branched alkyl, X¹²-cycloalkyl, -X¹²COOR⁶,

15

-X¹²CONR⁴R⁵, -X¹²N(R⁴)₂, or X¹²OR⁶;

20

R² is substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, carboxyl, nitro or -CF₃); -X¹²COOR⁶; 2-, 3-, 4-pyridyl;

25

R³ is $\begin{array}{c} \text{H} \quad \text{O} \\ | \quad || \\ \text{N}-\text{CR}^7 \end{array}$ or $\begin{array}{c} \text{H} \quad \text{O} \quad \text{H} \\ | \quad || \quad | \\ \text{N}-\text{C}-\text{NR}^7 \end{array}$ or $-\text{CR}^7$ or $\begin{array}{c} \text{O} \\ || \\ \text{N}-\text{CCH}_2\text{R}^7 \end{array}$;

30

R⁴ and R⁵ are independently R⁶ or in combination with the N of the NR⁴R⁵ group form an unsubstituted or mono- or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH₃ and the substituent(s) is/are independently selected from C₁₋₄ alkyl;

35

R⁶ is H, C₁₋₆ straight or branched-chain alkyl or cycloalkyl;

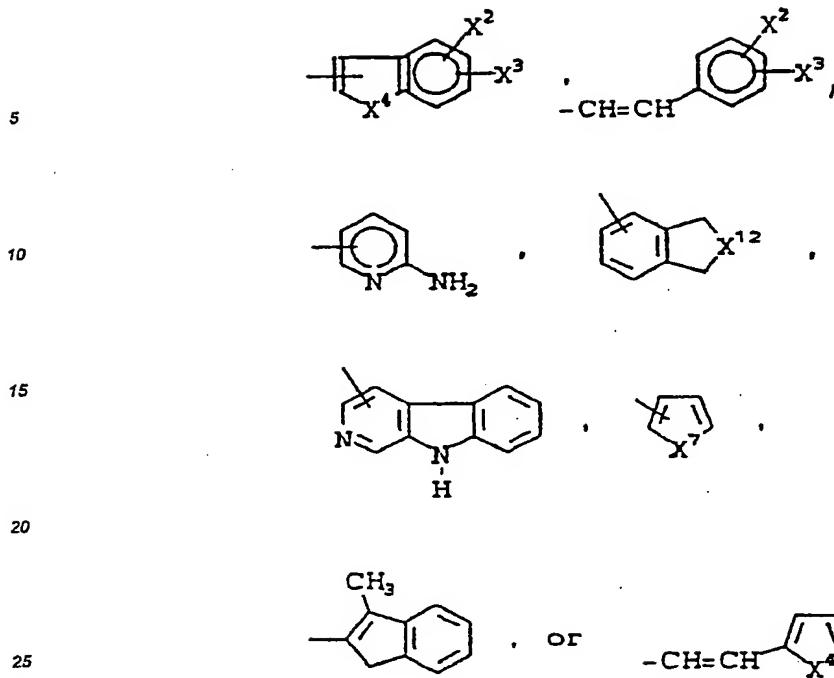
R⁷ is α- or β-naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, -NO₂, -OH, -NR⁴R⁵, loweralkyl, CF₃, CN, COOR⁶, X¹²COOR⁶, X¹²OR⁶, or loweralkoxy), 2-, 3-, 4-pyridyl,

40

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R⁸ is H, loweralkyl, cycloloweralkyl, X¹²COOR⁸;

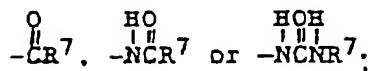
30 R¹⁰ is H or -OH where R³ is CR⁷, otherwise it is H;

35 r is 1 or 2;
X¹ is H, -NO₂, CF₃, loweralkyl or halo;
X² and X³ are independently H, -NO₂, OH, halo, loweralkyl, loweralkoxy, X¹²COOR⁸, COOR⁸, or OX¹²COOR⁸;
X⁴ is O, or NR⁸;
X⁷ is O;
40 X¹² is C₁₋₅ linear or branched chain alkyl, or the pharmaceutically acceptable salt thereof; for the preparation of a medicament useful for treating panic disorder or other neurological disorders involving anxiety.

45 9. The use as claimed in Claim 8 wherein:
R¹ is H, C₁-C₄ linear or branched chain alkyl, X¹²-cycloalkyl, -X¹²COOR⁸,

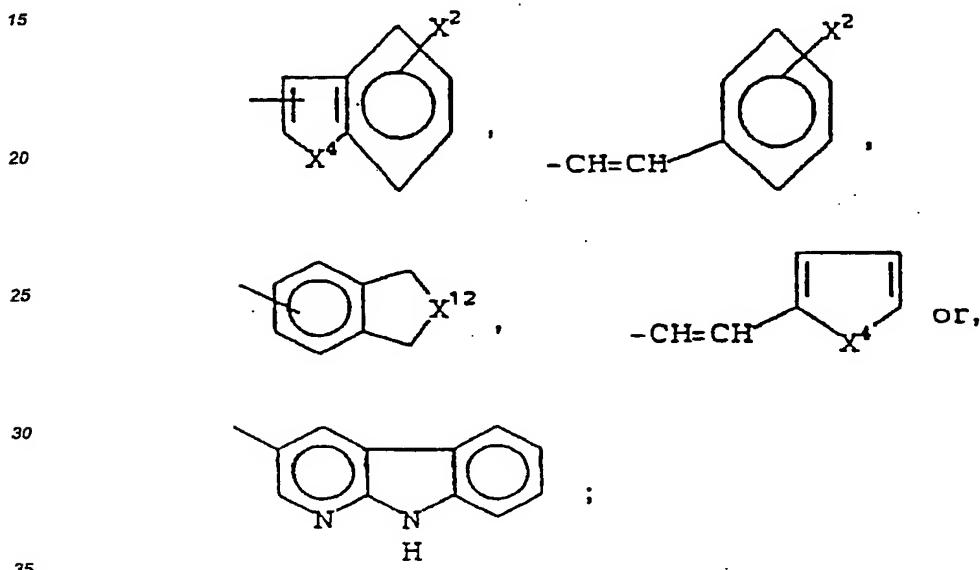
50 -X¹²CONR⁴R⁵, X¹²N⁵ R⁴ or X¹²OR⁶;

55 R² is substituted or unsubstituted phenyl (wherein the substituent may be 1 or 2 of halo, loweralkyl, nitro, -CF₃), 2,3,4-pyridyl, or X¹²COOR⁸;
R³ is



5 R^4 and R^5 are independently R^8 or in combination with the N of the NR^4R^5 group form an unsubstituted or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH_3 and the substituent(s) is/are independently selected from C_{1-4} alkyl ;

10 R^8 is H, C_{1-3} straight chain alkyl ;
 R^7 is α - or β -naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, $-\text{NO}_2$, NH_2 , methyl, ethyl, CF_3 , CN, COOH , X^{12}OR^8 , or lower alkoxy), 2,3,4-pyridyl,

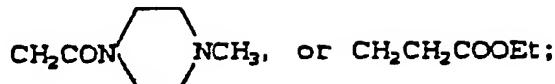
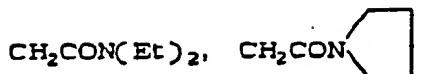


40 R^{10} is H, or OH when R^3 is CR^7 , otherwise R^{10} is H;
 τ is 1 or 2;

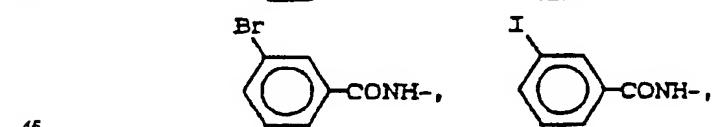
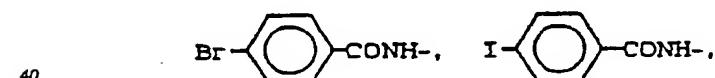
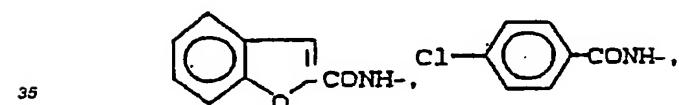
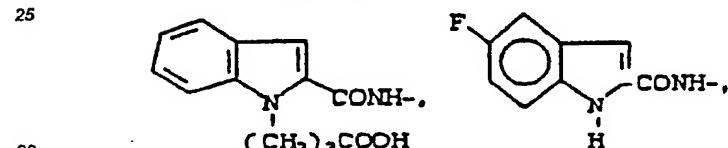
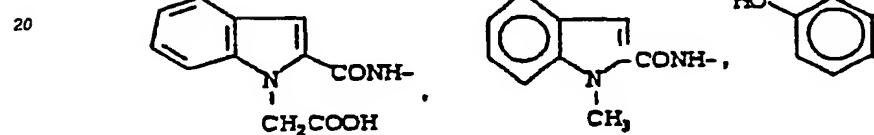
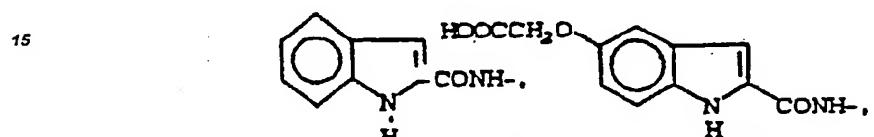
45 X^1 is H, $-\text{NO}_2$, CF_3 , loweralkyl or halo ;
 X^2 is H, $-\text{NO}_2$, halo, OH, loweralkoxy, loweralkyl, X^{12}COOH , or OCH_2COOH ;
 X^4 is O, NH, NCH_3 , $\text{NX}^{12}\text{COOH}$;
 X^7 is O ;
 X^{12} is C_{1-5} linear alkyl ; or pharmaceutically acceptable salt thereof.

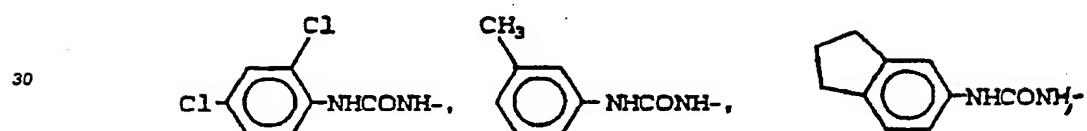
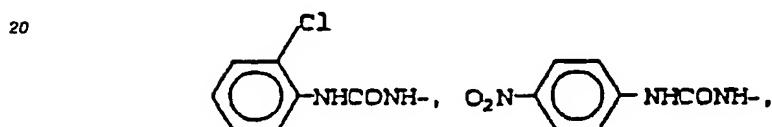
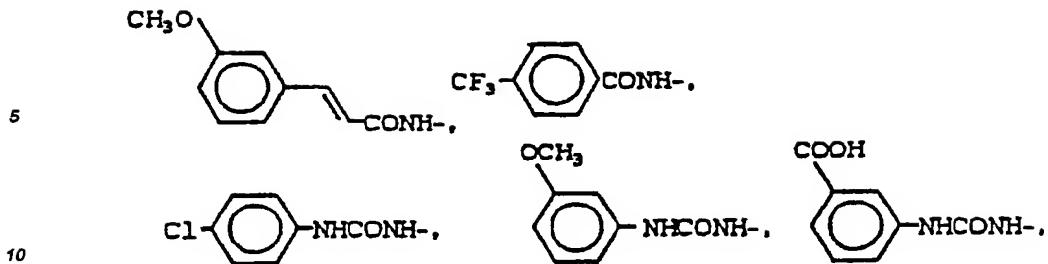
50 10. The use as claimed in Claim 9 wherein :

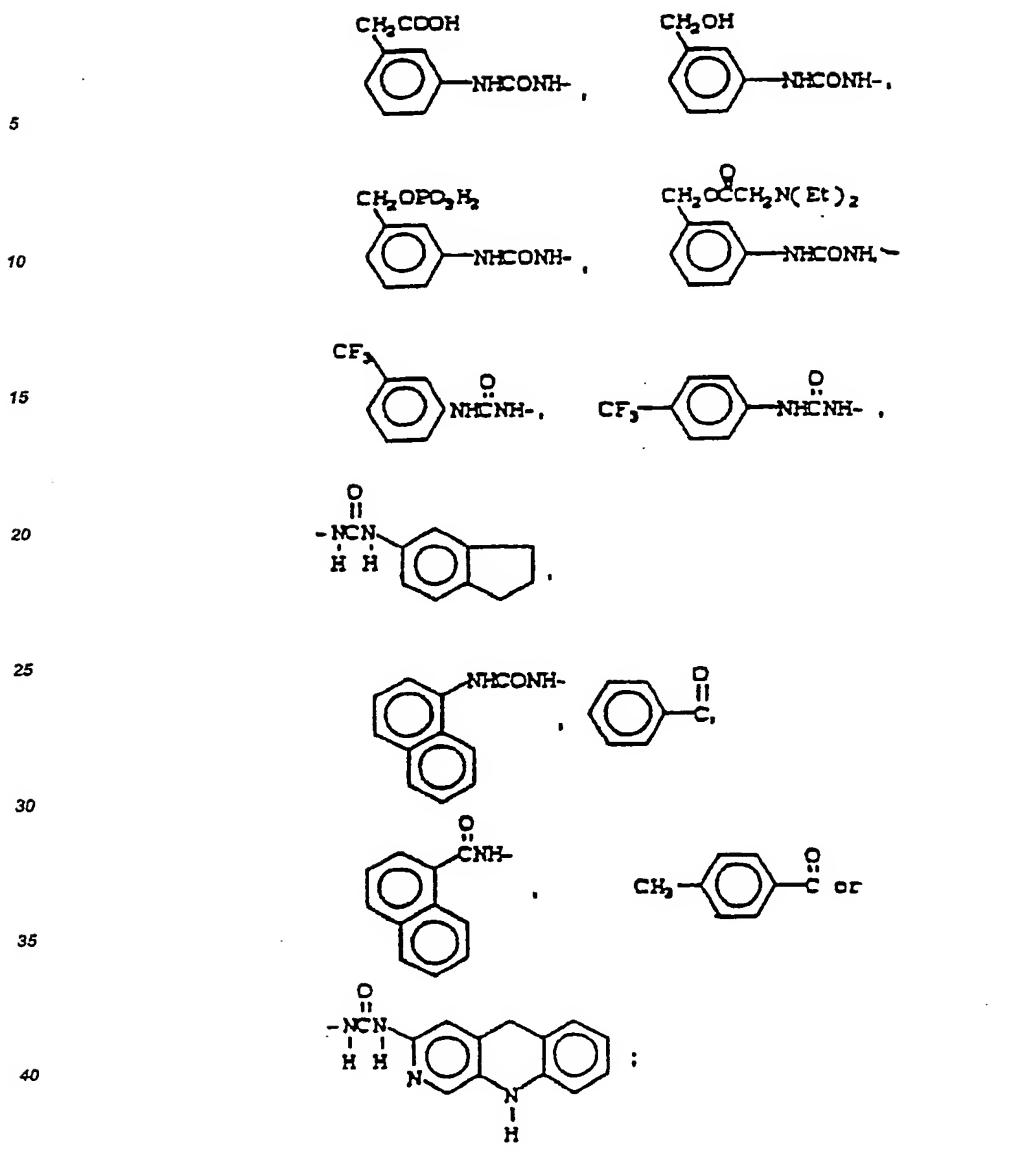
55 R^1 is H, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{---} \text{C}_6\text{H}_4\text{---}$,
 $-\text{CH}_2\text{CH}_2\text{OH}$, CH_2COOH , CH_2COOEt .



15 R^2 is phenyl, 2-F-phenyl, 4-CH₃-phenyl, 2-, 3-, or 4-pyridyl;
 R^3 is







50 R^{10} is H or -OH, when R^+ is the of CH_3 otherwise $R^{10}=H$;

X^1 is H, Cl ; or $-CH_3$;
 X^7 is O ;

55 11. The use of a CCK and or gastrin antagonist compound which is
3-N-(2,3-Dihydro-1-methyl-2-oxo-5-(p-tolyl)-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,
3-N-(2,3-Dihydro-1,9-dimethyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,

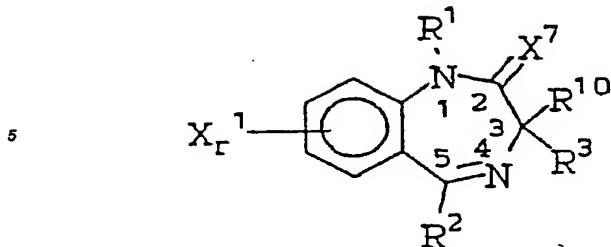
3-N-(2,3-Dihydro-1,8-dimethyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide, (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-3-phenyl-2-propenamide, (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(2-chlorophenyl)-urea, 1,3-Dihydro-3-(5-carboxymethoxyindole-2-carbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, 1,3-Dihydro-3-(5-hydroxyindole-2-carbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, (S)-N-(5-(2-Fluorophenyl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-4-(trifluoromethyl)-benzamide, 3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one, 3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one, 3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, 3-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-2-amino-4-chlorobenzamide, 4-Bromo-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-benzamide, 15 1,3-Dihydro-5-(2-fluorophenyl)-1-methyl-3(RS)-[2'-(1'-methylindole)carbonylamino]-2H-1,4-benzodiazepin-2-one, (S)-N-(2,3,-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methoxyphenyl)-urea, 1,3-dihydro-1-methyl-3(RS)-[2-(1-methylindole)-carbonylamino]-5-phenyl-2H-1,4-benzodiazepin-2-one, Carboxymethyl-1,3-dihydro-3(RS)-(2-indolecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one, 20 3(S)-(+)-1,3-Dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one, 3-[((3-Methoxyphenyl)amino)carbonyl]amino]-N,N-diethyl-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-acetamide, 1-((3-(((4-Chlorophenyl)amino)carbonyl)amino)-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-acetyl)pyrrolidine, (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea, 25 3-[((2-Chlorophenyl)amino)carbonyl]amino)-N,N-diethyl-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-acetamide, (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-bromophenyl)-urea, or (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(4-methylphenyl)-urea, (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxyphenyl)-urea, (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(5-indanyl)-urea, N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxymethylphenyl)urea, 30 (R)-N-(6-Amino-3-pyridinyl)-N'-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)urea, or N-(2,3-Dihydro-1-(2-hydroxyethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or pharmaceutically acceptable salt thereof ; for the preparation of a medicament useful for treating panic disorder or other neurological disorders involving anxiety.

12. The use as claimed in Claim 8, wherein the compound is 3(S)-(-)-1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, or (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or pharmaceutically acceptable salt thereof.

13. The use of the CCK and/or gastrin antagonist compound 3(S)-(-)-1,3-dihydro-3-(2-indolecarbonyl amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, or pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for treating panic disorder or other neurological disorders involving anxiety.

14. The use of the CCK and/or gastrin antagonist compound (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for treating panic disorder or other neurological disorders involving anxiety.

15. A pharmaceutical composition useful for directly inducing analgesia, anesthesia or loss of sensation of pain, comprising an effective amount of a CCK antagonist compound of the formula :



wherein :

R¹ is H, C₁₋₆ linear or branched alkyl, X¹²-cycloalkyl, -X¹²COOR⁸,

15

-X¹²CONR⁴R⁵, -X¹²N(R⁴)₂, or X¹²OR⁶;

20

R² is substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, carboxyl, nitro or -CF₃) ; -X¹²COOR⁶ ; 2-, 3-, 4-pyridyl ;

25

R³ is $\text{N}-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}=\overset{\text{O}}{\text{O}}-\text{R}^7$ or $\text{N}-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}=\overset{\text{O}}{\text{O}}-\text{R}^7$ or $\text{O}=\overset{\text{H}}{\underset{\text{H}}{\text{C}}}=\overset{\text{O}}{\text{O}}-\text{R}^7$ or $\text{N}-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}=\overset{\text{O}}{\text{O}}-\text{CH}_2-\text{R}^7$;

30

R⁴ and R⁵ are independently R⁸ or in combination with the N of the NR⁴R⁵ group form an unsubstituted or mono- or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH₃ and the substituent(s) is/are independently selected from C₁₋₄ alkyl ;

35

R⁸ is H, C₁₋₆ straight or branched-chain alkyl or cycloalkyl ;
R⁷ is α - or β -naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, -NO₂, -OH, -NR⁴R⁵, loweralkyl, CF₃, CN, COOR⁸, X¹²COOR⁸, X¹²OR⁶, or loweralkoxy), 2-, 3-, 4-pyridyl,

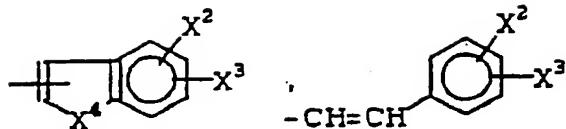
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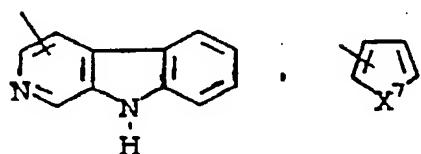


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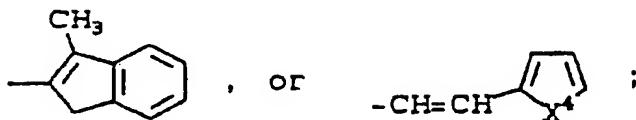


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30

R^8 is H, loweralkyl, cycloloweralkyl, $X^{12}COOR^8$;

35

R^{10} is H or $-OH$ where R^3 is CR^7 , otherwise it is H;
 τ is 1 or 2;

40

X^1 is H, $-NO_2$, CF_3 , loweralkyl or halo;
 X^2 and X^3 are independently H, $-NO_2$, OH, halo, loweralkyl, or loweralkoxy, $X^{12}COOR^8$, $COOR^8$, or $OX^{12}COOR^8$;

45

X^4 is O, or NR^8 ;

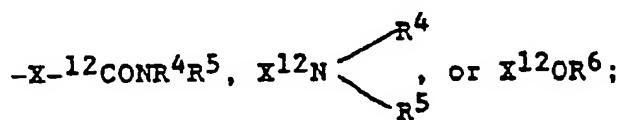
X^7 is O;

X^{12} is C_{1-5} linear or branched chain alkyl, or the pharmaceutically acceptable salt thereof.

16. The pharmaceutical composition of Claim 15 wherein :

R^1 is H, C_1-C_4 linear or branched chain alkyl, X^{12} -cycloalkyl, $-X^{12}COOR^8$,

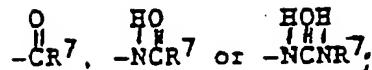
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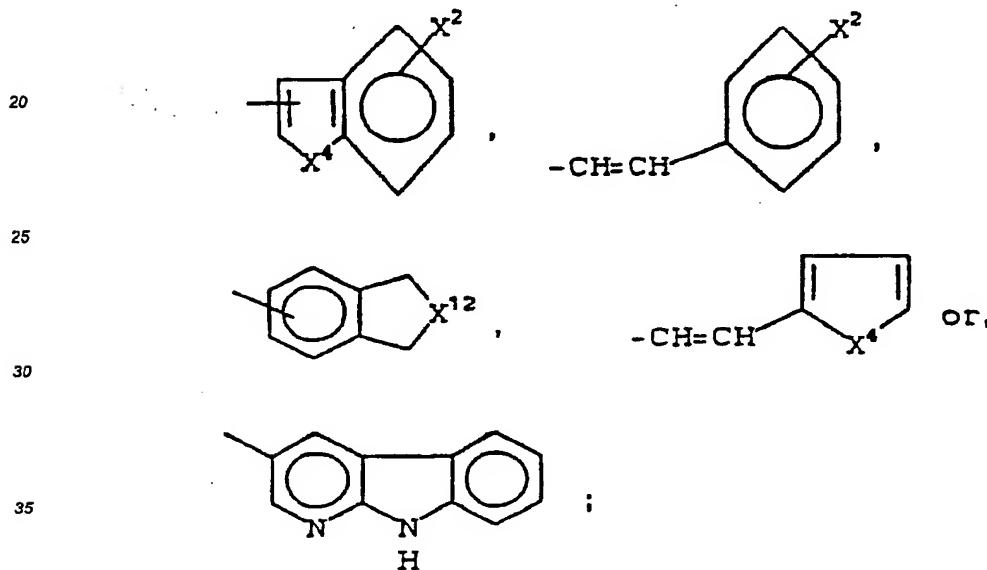
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R^2 is substituted or unsubstituted phenyl (wherein the substituent may be 1 or 2 of halo, loweralkyl, nitro, $-CF_3$, 2,3,4-pyridyl, or $X^{12}COOR^8$;

R^3 is



5 R^4 and R^5 are independently R^8 or in combination with the N of the NR^4R^5 group form an unsubstituted or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH_3 and the substituent(s) is/are independently selected from C_{1-6} alkyl ;
 10 R^8 is H, C_{1-3} straight chain alkyl ;
 R⁷ is α - or β -naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, $-\text{NO}_2$, NH_2 , methyl, ethyl, CF_3 ,
 15 CN , COOH ,
 X^{12}OR^8 , or lower alkoxy), 2-,3-,4-pyridyl,



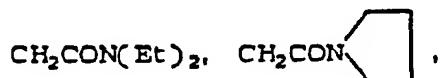
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 45 R^{10} is H, or OH when R^3 is CR^7 , otherwise R^{10} is H;

r is 1 or 2 ;
 X¹ is H, $-\text{NO}_2$, CF_3 , loweralkyl or halo ;
 X² is H, $-\text{NO}_2$, halo, OH, loweralkoxy, loweralkyl, X^{12}COOH , or OCH_2COOH ;
 X⁴ is O, NH, NCH_3 , X^{12}COOH ;
 X⁷ is O ;
 X¹² is C_{1-6} linear alkyl ;
 or pharmaceutically acceptable salt thereof.

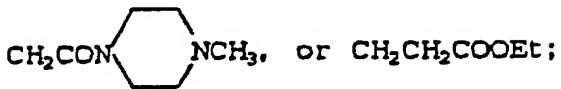
55 17. The pharmaceutical composition of Claim 16 wherein :

R^1 is H, CH_3 , CH_2CH_3 , $CH_2CH(CH_3)_2$, CH_2 — , CH_2CH_2OH , CH_2COOH , CH_2COOEt ,

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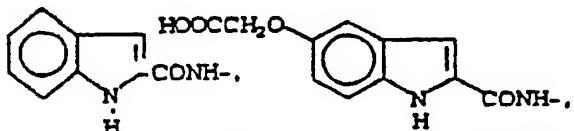
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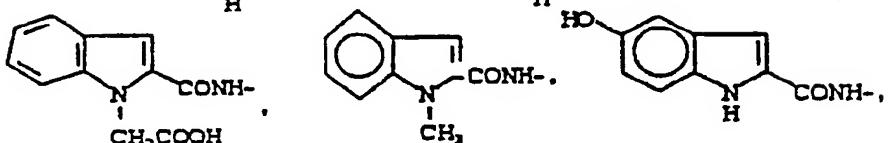
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R² is phenyl, 2-F-phenyl, 4-CH₃-phenyl, 2-, 3-, or 4-pyridyl ;
R³ is

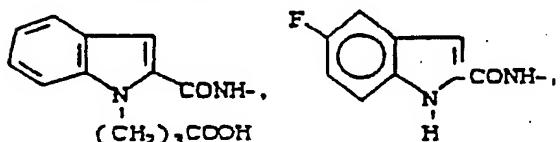
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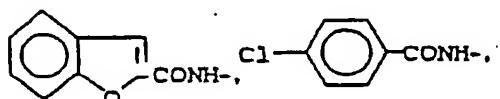
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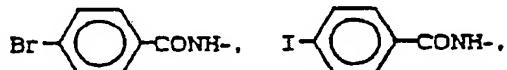
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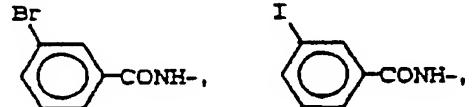
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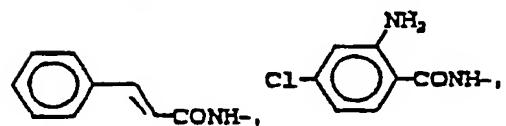
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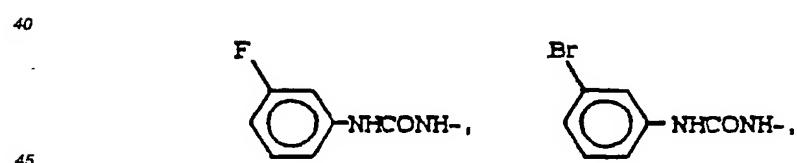
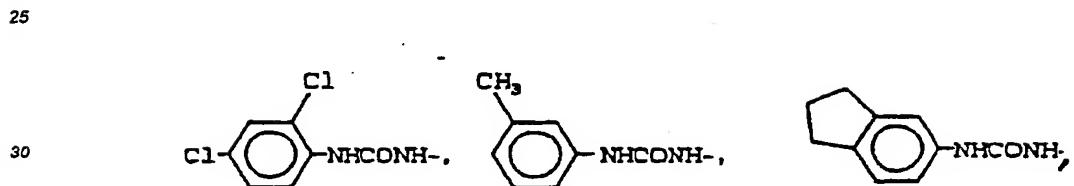
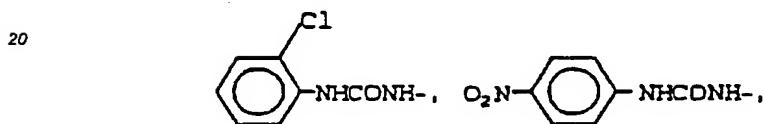
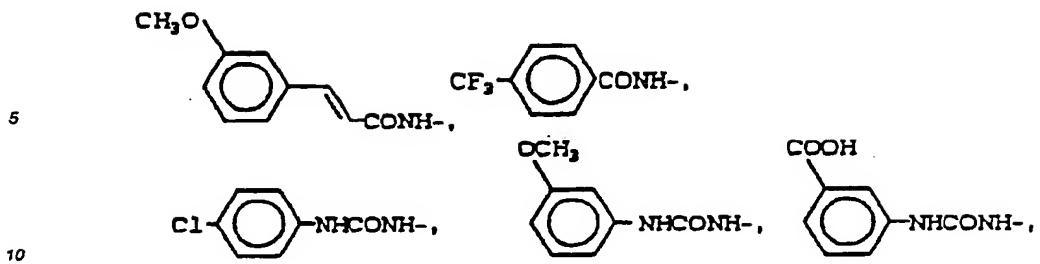
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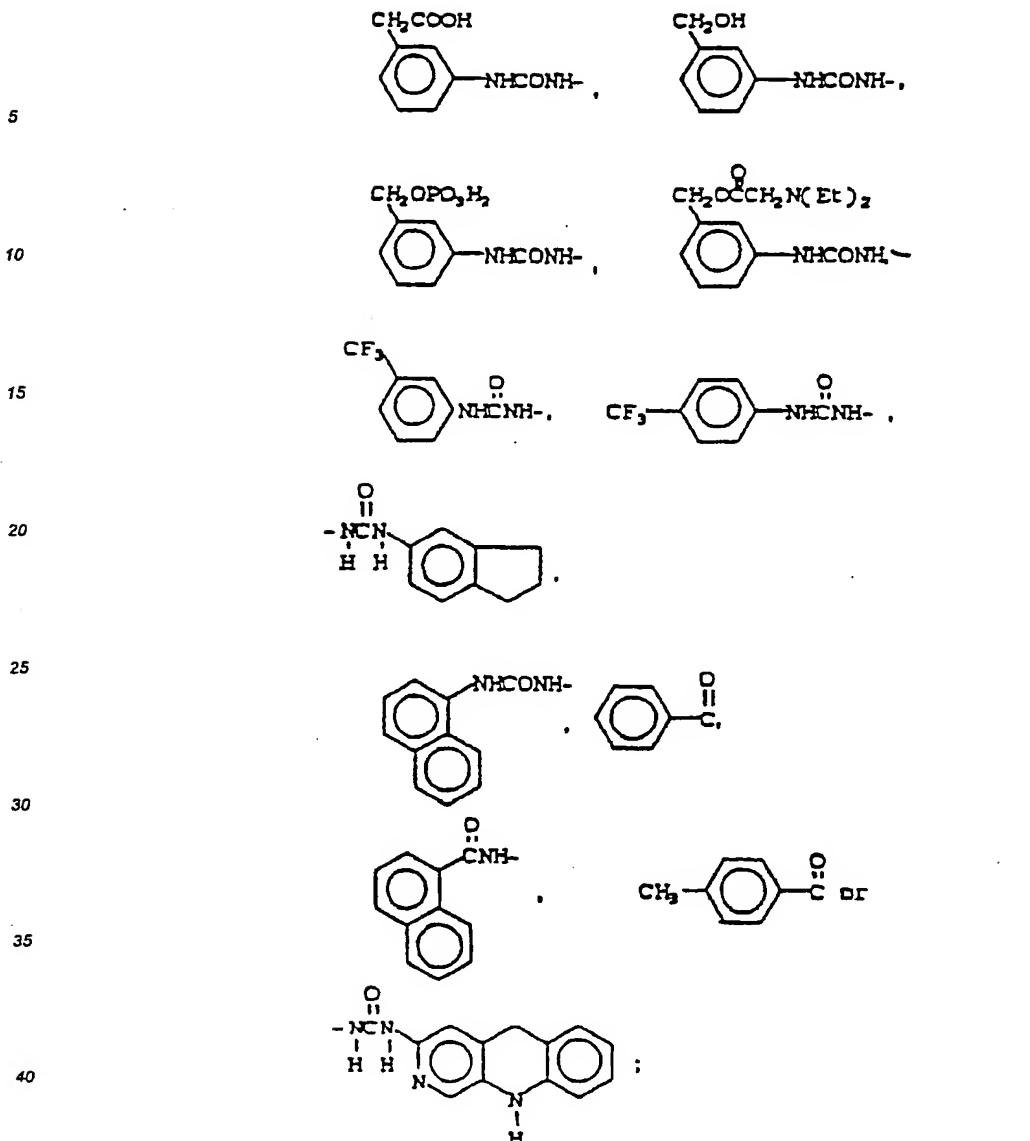


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50 R^{10} is H or $-OH$, when R^3 is PhC or CH_3 —— $C=O$,
otherwise $R^{10}=H$;

X^1 is H, Cl ; or $-CH_3$;
 X^7 is O ;

55 or pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition useful for directly inducing analgesia, anesthesia or loss of sensation of pain,

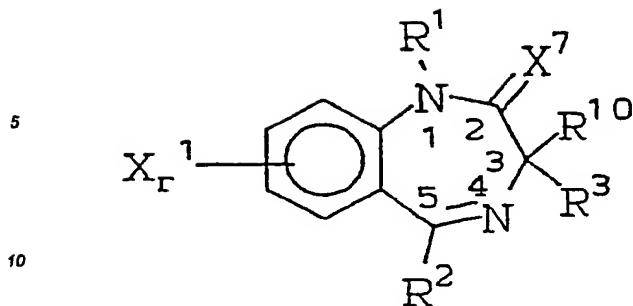
comprising an effective amount of a CCK antagonist compound which is
 3-N-(2,3-Dihydro-1-methyl-2-oxo-5-(p-tolyl)-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,
 3-N-(2,3-Dihydro-1,9-dimethyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,
 3-N-(2,3-Dihydro-1,8-dimethyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide,
 5 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-3-phenyl-2-propenamide,
 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(2-chlorophenyl)-urea,
 10 1,3-Dihydro-3-(5-carboxymethoxyindole-2-carbonyl-amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one,
 1,3-Dihydro-3-(5-hydroxyindole-2-carbonyl-amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one,
 15 (S)-N-(5-(2-Fluorophenyl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-4-(trifluoromethyl)-benzamide,
 3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-indolecarbonyl-amino)-1-methyl-2H-1,4-benzodiazepin-2-one,
 3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoyl-amino)-1-methyl-2H-1,4-benzodiazepin-2-one,
 3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonyl-amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one,
 20 3-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-2-amino-4-chlorobenzamide,
 4-Bromo-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-benzamide,
 1,3-Dihydro-5-(2-fluorophenyl)-1-methyl-3(RS)-[2'-(1'-methylindole)carbonyl-amino]-2H-1,4-benzodiazepin-2-one,
 25 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methoxyphenyl)-urea,
 1,3-dihydro-1-methyl-3(RS)-[2-(1-methylindole)-carbonyl-amino]-5-phenyl-2H-1,4-benzodiazepin-2-one,
 Carboxymethyl-1,3-dihydro-3(RS)-(2-indolecarbonyl-amino)-5-phenyl-2H-1,4-benzodiazepin-2-one,
 3(S)-(+)-1,3-Dihydro-3-(4-chlorobenzoyl-amino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one,
 30 3-[[((3-Methoxyphenyl)amino)carbonyl]amino]-N,N-diethyl-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-acetamide,
 1-((3-(((4-Chlorophenyl)amino)carbonyl)amino)-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-acetyl)pyrrolidine,
 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea,
 35 3-[[((2-Chlorophenyl)amino)carbonyl]amino]-N,N-diethyl-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-acetamide,
 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-bromophenyl)-urea, or
 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(4-methylphenyl)-urea,
 (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxyphenyl)-urea,
 40 (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(5-indanyl)-urea,
 N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxymethylphenyl)urea,
 (R)-N-(6-Amino-3-pyridinyl)-N'-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)urea, or
 N-(2,3-Dihydro-1-(2-hydromethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea,
 or pharmaceutically acceptable salt thereof.

45 19. The pharmaceutical composition of Claim 15, wherein the compound is
 3(S)-(-)-1,3-dihydro-3-(2-indolecarbonyl-amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, or (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition useful for directly inducing analgesia, anesthesia or loss of sensation of pain, comprising an effective amount of the CCK and/or gastrin antagonist compound 3(S)-(-)-1,3-dihydro-3-(2-indolecarbonyl amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, or pharmaceutically acceptable salt thereof.

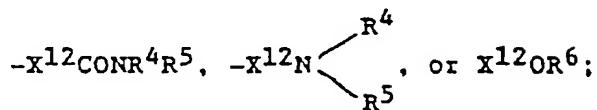
50 21. A pharmaceutical composition useful for directly inducing analgesia, anesthesia or loss of sensation of pain, comprising an effective amount of the CCK and/or gastrin antagonist compound (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or pharmaceutically acceptable salt thereof.

55 22. The use of a CCK antagonist compound of the formula :



wherein

15 R¹ is H, C₁₋₆ linear or branched alkyl, X¹²-cycloalkyl, -X¹²COOR⁶,



25 R² is substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, carboxyl, nitro or -CF₃);
 -X¹²COOR⁶; 2-, 3-, 4-pyridyl;

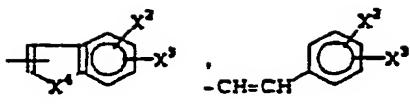


35 R⁴ and R⁵ are independently R⁶ or in combination with the N of the NR⁴R⁵ group form an unsubstituted or mono- or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may contain a second heteroatom selected from O and NCH₃ and the substituent(s) is/are independently selected from C₁₋₄ alkyl;
 R⁶ is H, C₁₋₆ straight or branched-chain alkyl or cycloalkyl;
 R⁷ is α- or β-naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, -NO₂, -OH, -NR⁴R⁵, loweralkyl, CF₃, CN, COOR⁶, X¹²COOR⁶, X¹²OR⁶, or loweralkoxy), 2-, 3-, 4-pyridyl.

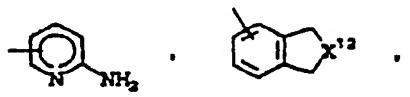
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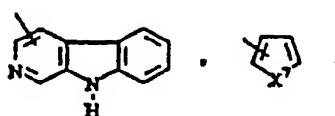
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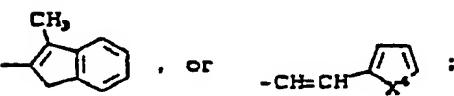
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R⁸ is H, loweralkyl, cycloloweralkyl, X¹²COOR⁶;

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R¹⁰ is H or -OH where R³ is CR⁷, otherwise it is H;

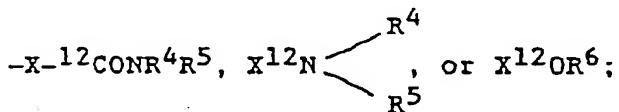
r is 1 or 2;

30 X¹ is H, -NO₂, CF₃, loweralkyl or halo;
 X² and X³ are independently H, -NO₂, OH, halo, loweralkyl, or loweralkoxy, X¹²COOR⁶, COOR⁶, or OX¹²COOR⁶;
 X⁴ is O, or NR⁸;
 X⁷ is O;
 35 X¹² is C₁₋₆ linear or branched chain alkyl,
 or the pharmaceutically acceptable salt thereof; for the preparation of a medicament useful for directly inducing analgesia, anesthesia or loss of sensation of pain.

23. The use as claimed in Claim 22 wherein:

40 R¹ is H, C_{1-C₄} linear or branched chain alkyl, X¹²-cycloalkyl, -X¹²COOR⁶,

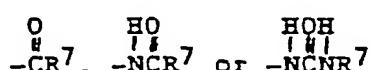
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R² is substituted or unsubstituted phenyl (wherein the substituent may be 1 or 2 of halo, loweralkyl, nitro, -CF₃), 2-,3-,4-pyridyl, or X¹²COOR⁶;

R³ is



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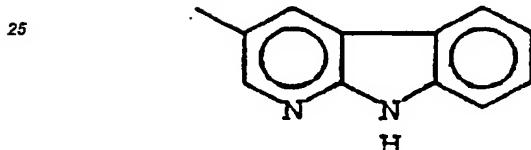
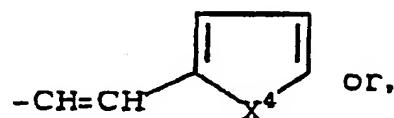
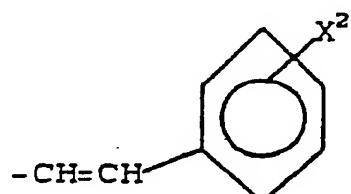
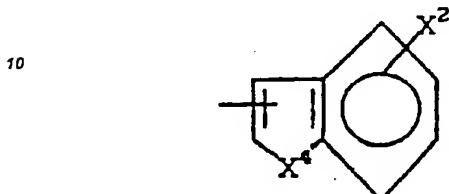
R⁴ and R⁵ are independently R⁶ or in combination with the N of the NR⁴R⁵ group form an unsubstituted or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring wherein said heterocyclic ring or said benzofused heterocyclic ring may

contain a second heteroatom selected from O and NCH₃ and the substituent(s) is/are independently selected from C₁₋₄ alkyl;

R⁶ is H, C₁-C₃ straight chain alkyl;

R⁷ is α - or β -naphthyl, substituted or

5 unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, -NO₂, NH₂, methyl, ethyl, CF₃, CN, COOH, X¹²OR⁶, or loweralkoxy, 2-,3-,4-pyridyl,



;

35 R¹⁰ is H, or OH when R³ is CR⁷, otherwise R¹⁰ is H;

40 r is 1 or 2;

X¹ is H, -NO₂, CF₃, loweralkyl or halo;

X² is H, -NO₂, halo, OH, loweralkoxy, loweralkyl, X¹²COOH, or OCH₂COOH;

X⁴ is O, NH, NCH₃, NX¹²COOH;

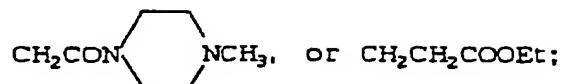
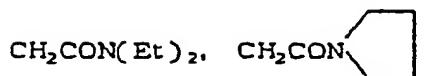
X⁷ is O;

X¹² is C₁₋₆ linear alkyl;

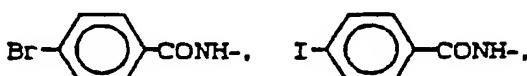
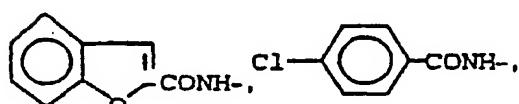
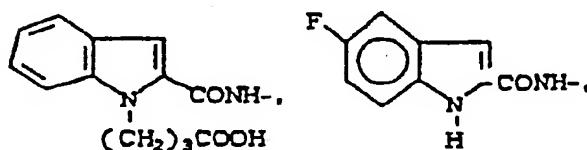
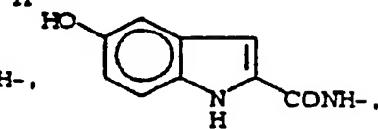
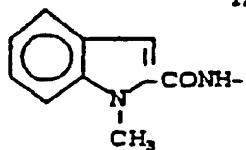
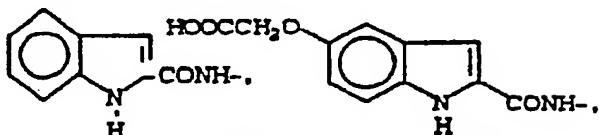
or pharmaceutically acceptable salt thereof.

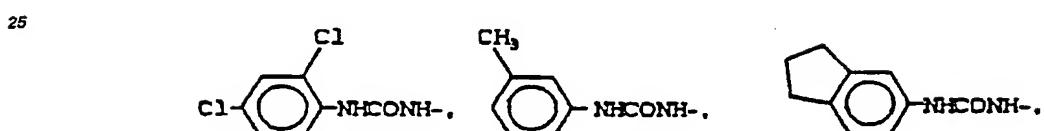
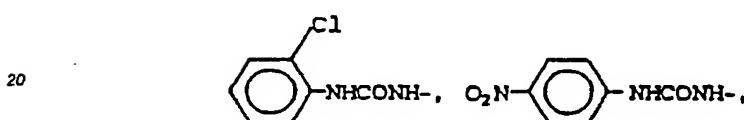
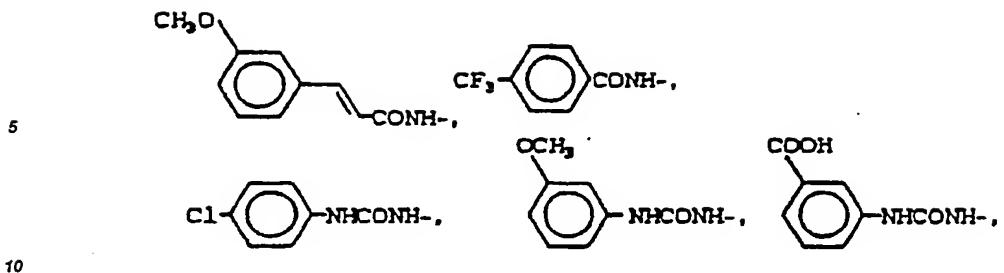
45 24. The use as claimed in Claim 23 wherein :

50 R¹ is H, CH₃, CH₂CH₃, CH₂CH(CH₃)₂, CH₂— ,
CH₂CH₂OH, CH₂COOH, CH₂COOEt,



15 R^2 is phenyl, 2-F-phenyl, 4-CH₃-phenyl, 2-, 3-, or 4-pyridyl ;
 R^3 is

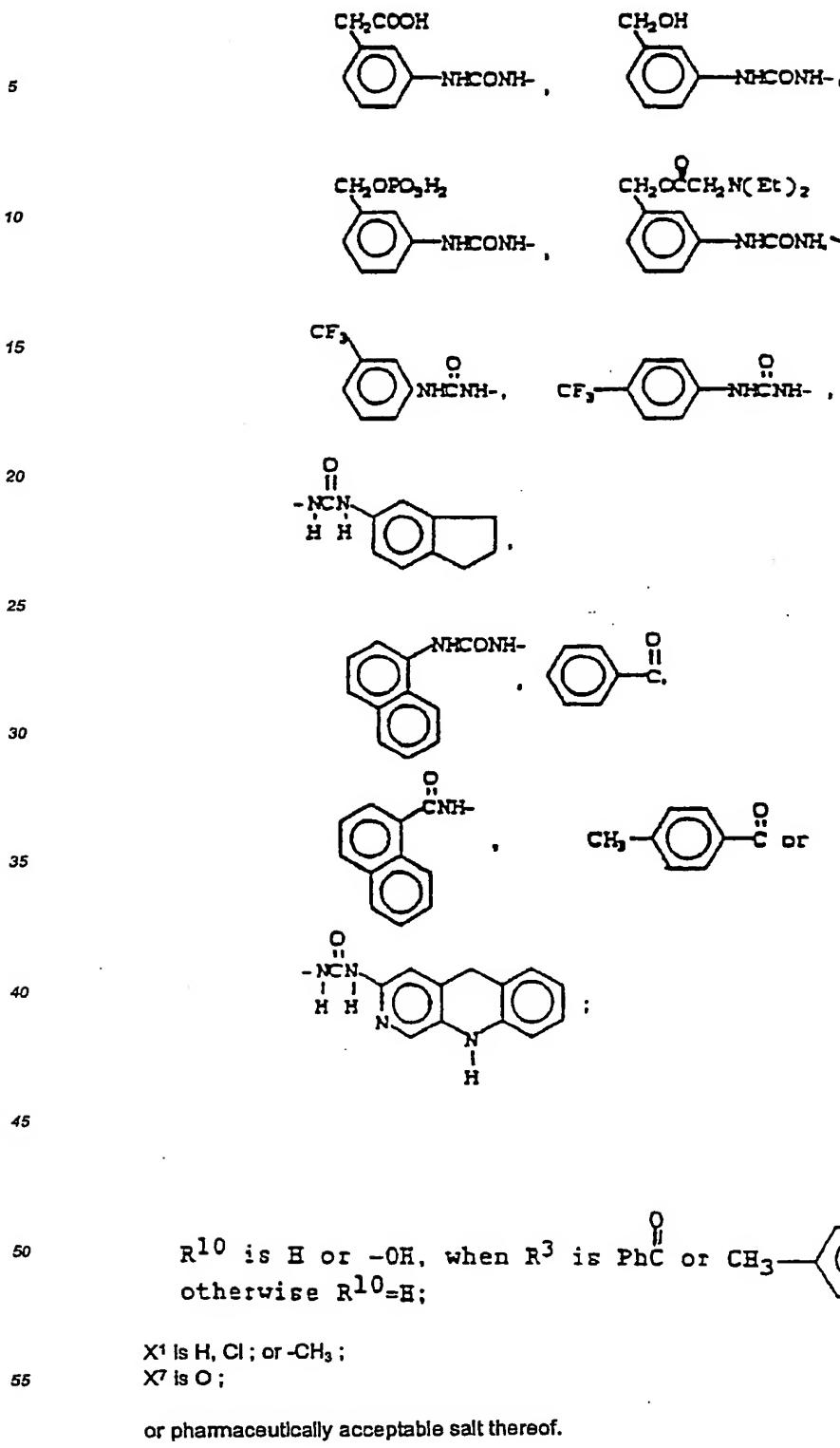




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25. The use of a CCK antagonist compound for the preparation of a medicament useful for directly inducing analgesia, anesthesia or loss of sensation of pain, wherein the CCK antagonist compound is :
 3-N-(2,3-Dihydro-1-methyl-2-oxo-5-(p-tolyl)-1H-1,4-benzodiazepin-3-yl)-1H-Indole-2-carboxamide,
 3-N-(2,3-Dihydro-1,9-dimethyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-Indole-2-carboxamide,
 3-N-(2,3-Dihydro-1,8-dimethyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-Indole-2-carboxamide,
 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-3-phenyl-2-propenamide,
 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(2-chlorophenyl)-urea,
 1,3-Dihydro-3-(5-carboxymethoxyindole-2-carbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one,
 1,3-Dihydro-3-(5-hydroxyindole-2-carbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one,
 (S)-N-(5-(2-Fluorophenyl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl)-4-(trifluoromethyl)-benzamide,
 3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-one,
 3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one,
 3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one,
 3-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-2-amino-4-chlorobenzamide,
 4-Bromo-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-benzamide,
 1,3-Dihydro-5-(2-fluorophenyl)-1-methyl-3(RS)-[2'-(1'-methylindole)carbonylamino]-2H-1,4-benzodiazepin-2-one,
 (S)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methoxyphenyl)-urea,
 1,3-dihydro-1-methyl-3(RS)-[2-(1-methylindole)-carbonylamino]-5-phenyl-2H-1,4-benzodiazepin-2-one,
 Carboxymethyl-1,3-dihydro-3(RS)-(2-indolecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one,
 3(S)-(+)-1,3-Dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one,
 3-[(((3-Methoxyphenyl)amino)carbonyl)amino]-N,N-diethyl-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-acetamide,
 1-(((4-Chlorophenyl)amino)carbonyl)amino)-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-yl)-acetyl)pyrrolidine,
 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-urea,
 3-(((2-Chlorophenyl)amino)carbonyl)amino)-N,N-diethyl-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-1-acetamide,
 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-bromophenyl)-urea, or
 (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(4-methylphenyl)-urea,
 (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxyphenyl)-urea,
 (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(5-indanyl)-urea,
 N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-carboxymethylphenyl)urea,
 (R)-N-(6-Amino-3-pyridinyl)-N'-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)urea, or
 N-(2,3-Dihydro-1-(2-hydroxyethyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or pharmaceutically acceptable salt thereof.

26. The use as claimed in Claim 22, wherein the compound is
 3(S)-(-)-1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, or
 (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or pharmaceutically acceptable salt thereof.

27. The use of the CCK and/or gastrin antagonist compound 3(S)-(-)-1,3-dihydro-3-(2-indolecarbonyl amino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, or pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for directly inducing analgesia, anesthesia or loss of sensation of pain.

28. The use of the CCK and/or gastrin antagonist compound (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea, or pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for directly inducing analgesia, anesthesia or loss of sensation of pain.

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